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THE PHYSICAL FINDINGS IN PERICARDITIS WITH EFFUSION. By ROGER S. MORRIS, M.D., and CARL F. LITTLE, M.D. 625

STRUCTURAL AND FUNCTIONAL INVOLVEMENT OF THE HEART FOLLOWING ACUTE RESPIRATORY AND OTHER ACUTE INFECTIONS. (SECOND PAPER.) By WALTER W. HAMBURGER, M.D., and WALTER, S. PRIEST, JR., M.D. 629

DETAILS IN THE TREATMENT OF HAY-FEVER, ASTHMA AND OTHER MANIFESTATIONS OF ALLERGY. By W. W. DUKE, M.D. 645

NON-SPECIFIC VERSUS SPECIFIC THERAPY IN BRONCHIAL ASTHMA. By NATHAN S. SCHIFF, M.D. 664

THE DURATION AND MAGNITUDE OF THE HYPOGLYCEMIA AFTER INSULIN. By ELMER L. SEVRINGHAUS, M.D., ELIZABETH KIRK, and HAROLD J. HEATH . . . 677

A REPORT OF SIXTY-FOUR CASES OF DIABETES MELLITUS TREATED WITH INSULIN. By LEON JONAS, M.D. 687

THE TREATMENT OF DIABETIC COMA WITH INSULIN. By NELLIS B. FOSTER, M.D. 699

ILEOCECAL INCOMPETENCE: A CLINICAL ANALYSIS OF 1000 CASES WITH SOME DEDUCTIONS THEREFROM. By NOBLE WILEY JONES, M.D. 710

EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS, AS DEDUCED FROM A MILD EPIDEMIC OCCURRING IN THE 8TH CORPS AREA, MARCH, 1922. By LEWIS B. BIBB, M.D. 731

THE USE OF GENTIAN VIOLET IN THE TREATMENT OF EMPYEMA. By ROBERT C. DAVIS, M.D. 743

BUSINESS OPENING FOR PHYSICIAN . . . . . ADV. PAGE 10

INDEX TO ADVERTISERS . . . . . " " 35

Contents continued on page x

OWNERS AND PUBLISHERS
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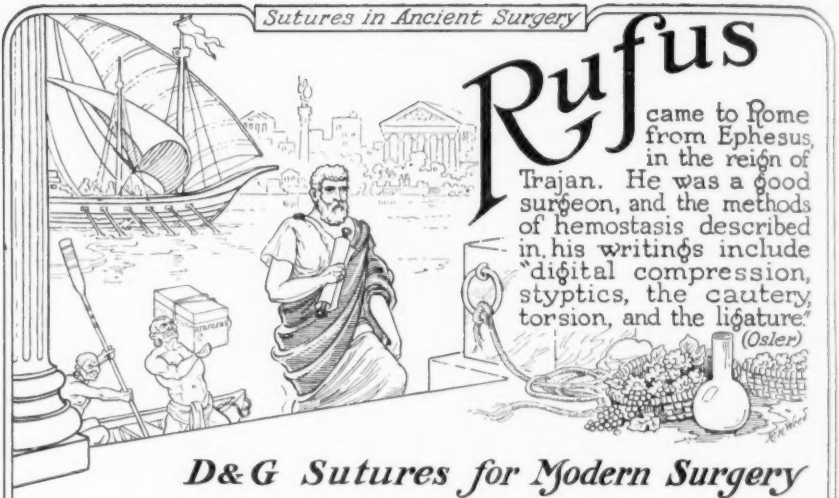

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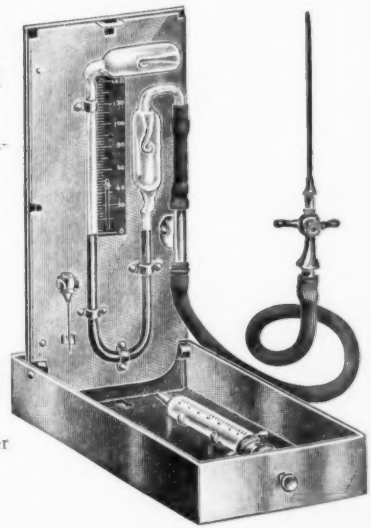

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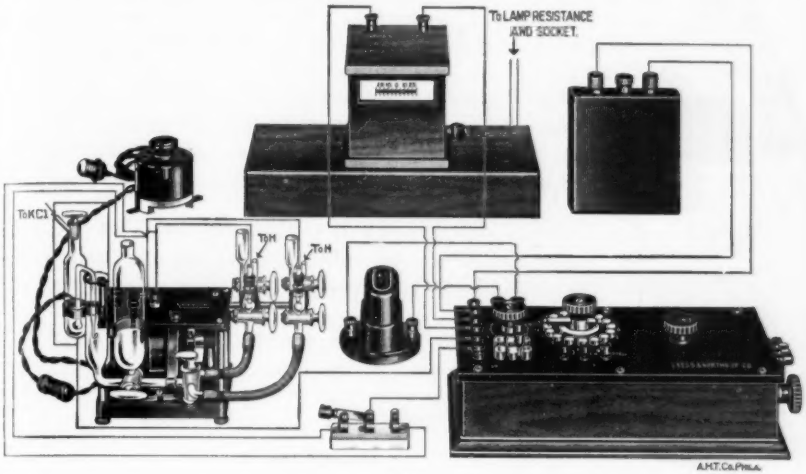

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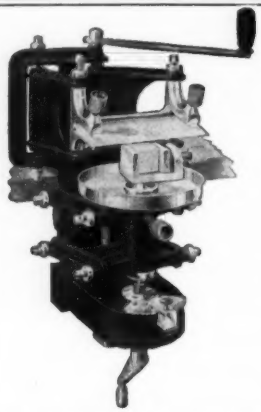

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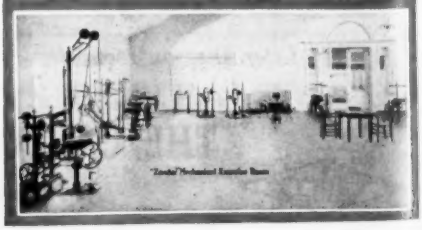

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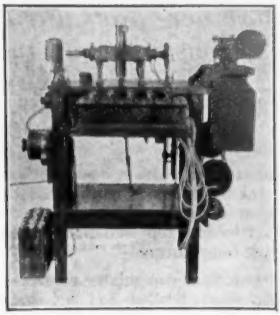

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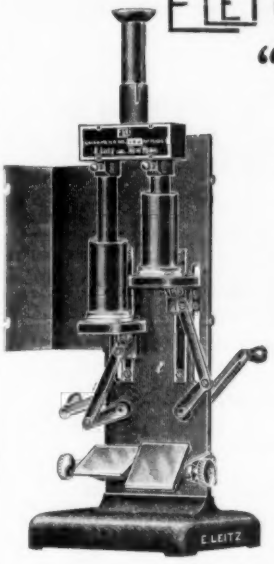

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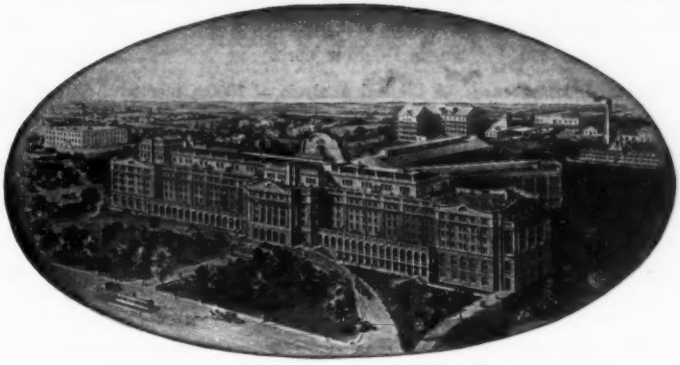

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CONTENTS

ORIGINAL ARTICLES

The Physical Findings in Pericarditis with Effusion 625
By Roger S. Morris, M.D., and Carl F. Little, M.D., Cincinnati, Ohio.

Structural and Functional Involvement of the Heart Following Acute Respiratory and Other Acute Infections (Second Paper) . . . 629
By Walter W. Hamburger, M.D., and Walter S. Priest, Jr., M.D., Chicago, Ill.

Details in the Treatment of Hay-fever, Asthma and Other Manifestations of Allergy 645
By W. W. Duke, M.D., Kansas City, Mo.

Non-specific versus Specific Therapy in Bronchial Asthma 664
By Nathan S. Schiff, M.D., New York.

The Duration and Magnitude of the Hypoglycemia after Insulin . . 677
By Elmer L. Sevringhaus, M.D., Elizabeth Kirk and Harold J. Heath, Madison, Wis.

A Report of Sixty-four Cases of Diabetes Mellitus Treated with Insulin 687
By Leon Jonas, M.D., Philadelphia.

The Treatment of Diabetic Coma with Insulin 699
By Nellis B. Foster, M.D., New York.

Ileocecal Incompetence: A Clinical Analysis of 1000 Cases with Some Deductions Therefrom 710
By Noble Wiley Jones, M.D., Portland, Ore.

Epidemiology of Acute Respiratory Infections, As Deduced from a Mild Epidemic Occurring in the 8th Corps Area, March, 1922 . . . 731
By Lewis B. Bibb, M.D., Carlisle Barracks, Pa.

The Use of Gentian Violet in the Treatment of Empyema 743
By Robert C. Davis, M.D., Rosedale, Kans.

(*Contents continued on page 12*)

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REVIEWS

The Principles and Practice of Perimetry. By Luther C. Peter, M.D., F.A.C.S. . . . 751
Clinical Tuberculosis. By Francis Marion Pottenger, M.D. . . . 752
Bronchoscopy and Esophagoscopy. By Chevalier Jackson, M.D., F.A.C.S. . . . 753
International Clinics. Volume II . . . 753
The Determination of Hydrogen Ions. By W. Mansfield Clark, M.A., Ph.D. . . . 754
Papers from the Mayo Foundation and the Medical School of University of Minnesota, 1921–1922. Volume II. . . . 754
Epidemiology and Public Health (A Text and Reference Book for Physicians, Medical Students and Health Workers; in Three Volumes). Volume II: Nutritional Disorders, Alimentary Infections, Percutaneous Infections. By Victor C. Vaughan, M.D., LL.D., assisted by Henry F. Vaughan, M.S., Dr. P.H., and George T. Palmer, M.S., Dr. P.H. . . . 755
Die Medizin der Gegenwart in Selbstdarstellungen. Edited by Prof. Dr. L. R. Grote . . . 755
Practical Dietetics. By Alida Frances Pattee . . . 756
Contributions from the Peking Union Medical College, Peking, China. Volume II . . . 756
The Dominant Sex. By Mathilde and Mathias Vaerting. Translated from the German by Eden and Cedar Paul . . . 757
Optotypes. Seventeen Test Letters and Pictographs. By Green and Ewing . . . 757
Annals of Roentgenology. A Series of Monographic Atlases. Edited by James T. Case, M.D. Volume III: Digestive Disturbances in Infants and Children Roentgenologically Considered. By Charles Gilmore Kerley, M.D., and Leon Theodore Lewald, M.D. . . . 758
Physiotherapy Technic: A Manual of Applied Physics. By C. M. Sansom, M.D. . . . 758

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The Neutralization of Tetanus Antitoxin with Nucleic Acid . . . 759
Value of Phenoltetrachlorphthalein on Estimating Liver Function . . . 759
Amebic Bronchitis without Abscess . . . 760
The Effects of Quinidine upon Paroxysms of Tachycardia . . . 760
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(*Contents continued on page 14*)

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Studies on Tumor Formation (Heterotopic Tumors) . . . 762
Köhler's Disease of the Tarsal Scaphoid . . . 762
Syphilis of the Stomach . . . 762
Tuberculosis of the Epididymis . . . 762
Flow of Lymph from Ileocecal Angle and its Possible Bearing on the Cause of Duodenal and Gastric Ulcer . . . 763
Retrograde Intussusception of the Small Intestine after Gastro-enterostomy . . . 763
Loose Bodies in Joints . . . 763
Experimental Incision in the Cadaver for Drainage of the Ankle-joint . 764
An Electrochemical Interpretation of Shock and Exhaustion . . . 764
Renal Hemorrhages (Postoperative) . . . 764
Brain Abscess . . . 764
The Transfusion of Unmodified Blood . . . 765
Upon Operation for Ischiorectal Fistula . . . 765

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.

A Seasonal Tide of Blood Phosphates in Infants . . . 765
The Mechanism and Fundamental Causes of Epilepsy . . . 766
The Treatment of Acute Poliomyelitis . . . 767
Health and Nutrition Work Among Children of the Preschool Age . . 767
The Value of the Toxin (Antigen) of Rhus Toxicodendron and Rhus Venenata in the Treatment and Desensitization of Patients with Dermatitis Venenata . . . 768

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.

Repeated Dystocia from Fetal Anomaly in Successive Pregnancies . . 768
A Successful Test for Liver Function in Pregnancy and its Toxemia . 770
Pregnancy and Labor After the Operative Replacement of the Inverted Uterus . . . 770
Injury in Labor to the Brain of the Newborn . . . 771
Prenatal Care . . . 771

(*Contents continued on page 16*)

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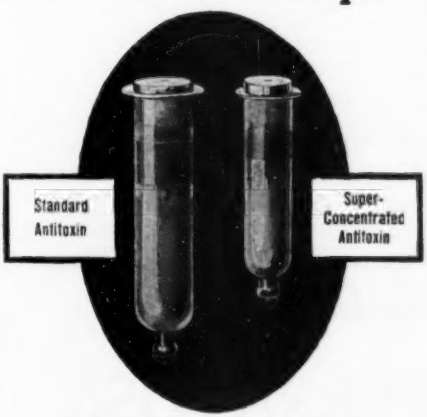

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JOHN G. CLARK, M.D., AND FRANK B. BLOCK, M.D.

Relation of Cell Type to Degree of Malignancy in Cancer of Cervix . 771
Modification of Rubin Technic for Tubal Inflation 773

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M., AND DE WAYNE G. RICHEY, B.S., M.D.

Types of Canine Anaphylaxis 774
On Isohemagglutination 774
A Hitherto Undescribed Pair of Isoagglutination Elements in Human Beings 775
A Dangerous "Universal Donor" Detected by the Direct Matching of Bloods 775
The Endothelial Factor in Anaphylaxis 776
Anaphylactic Reactions on Isolated Canine Organs 776
An Anaërobe from the Mouth Cavity of Man and Rabbits Morphologically Suggesting B. Pneumosintes 777

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D., AND GEORGE W. McCOY, M.D.

Botulism. Studies on the Manner in Which the Toxin of Clostridium Botulinum Acts upon the Body. I. The Effect upon the Autonomic Nervous System 778
Experimental Observations on the Prophylaxis and Treatment of Syphilis 778
Obesity: Observations on One Thousand Cases 779
Dengue Fever. A Clinical Report of the Galveston Epidemic of 1922 . 779
Weil-Felix Reaction in Rocky Mountain Spotted Fever 779
Experimental Abortion in a Cow Produced by Inoculation with Bacterium Melitensis 779
A Report on the Indigent Migratory Consumptive in Certain Cities of the Southwest 779
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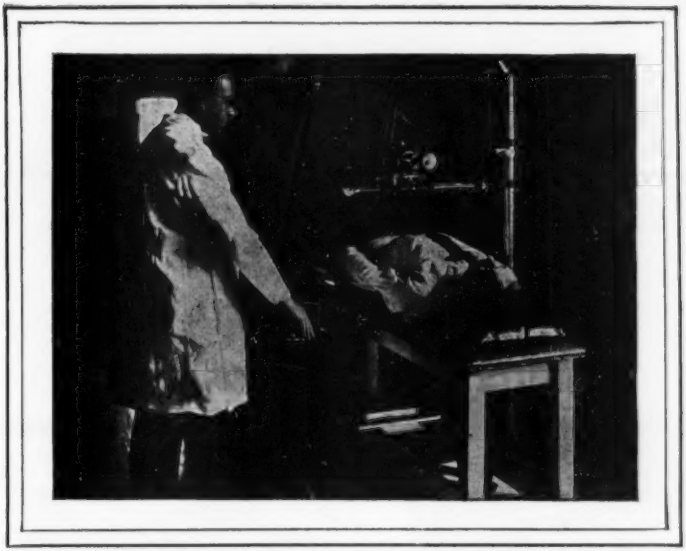

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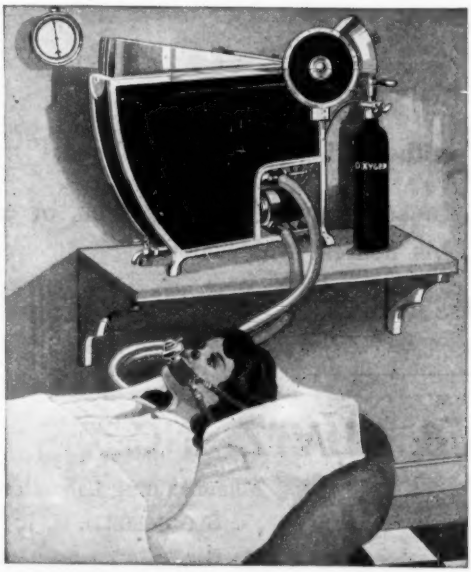

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AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

NOVEMBER, 1923

ORIGINAL ARTICLES.

THE PHYSICAL FINDINGS IN PERICARDITIS WITH EFFUSION.[1]

By Roger S. Morris, M.D.

TAYLOR PROFESSOR OF MEDICINE,

AND

Carl F. Little, M.D.

ASSOCIATE PROFESSOR OF ROENTGENOLOGY, UNIVERSITY OF CINCINNATI COLLEGE OF MEDICINE, CINCINNATI, OHIO.

From the Medical Clinic and the Roentgenologic Laboratory of the Cincinnati General Hospital.)

The diagnosis of a pericardial effusion is often a matter of great difficulty. Even with the most painstaking physical examination, a large effusion may be missed, as all clinicians who follow their patients to the autopsy table realize. This fact indicates that the physical signs of pericardial effusion are not always distinctive, and led one of the writers (R. S. M.) and Bader[2] to study the problem experimentally.

In these experiments, ascitic fluid was injected into the pericardium of fresh cadavers within four hours after death. Particular attention was paid to the shape of the cardio-hepatic angle and to the shape and extent of the relative cardiac dulness and the cardiac shadow in radiograms. It was found that the cardio-hepatic angle is acute—at the most a right angle, but never obtuse in the injected pericardia—even after the introduction of 2 liters of fluid. The

[1] Presented at the meeting of the Association of American Physicians at Atlantic City, N. J., May 1, 1923.

[2] A Comparison of the Percussion and Roentgen-ray Findings after Injection of the Pericardium, Jour. Am. Med. Assn., 1917, **69**, 450.

least amount of fluid causing a change in the percussion findings was 250 cc (inconstant), but it was not until 500 cc had been injected that definite percussion and roentgen-ray changes could be detected with uniformity. It was further observed in the experimental injections that there is a marked widening of the retromanubrial dulness at the base of the heart, with a corresponding increase in width of the shadow in the radiograms, and, what is probably of greater practical importance, that the area of dulness and the extent of the shadow in this region decrease in width when the cadaver is changed from the recumbent to the erect posture.

The present report is the result of a continuation of the earlier work, but instead of cadavers, we have confined our observations to patients ill with pericarditis.

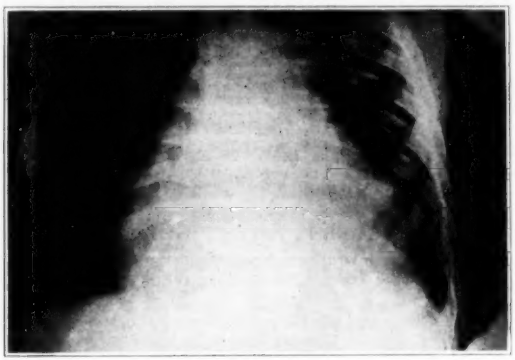

FIG. 1.—Teleroentgenogram pericarditis with effusion.

Our attention has been focussed again chiefly on the percussion findings, though we, like others, have been impressed with the fact that even with large accumulations of fluid in the pericardium, the apex impulse *may* remain visible and palpable and the heart sounds of good intensity throughout the course of the disease; and that, at times, a pericardial friction rub may persist along the left sternal border, near the base of the heart.

In many of the text-books on diagnosis, the statement is made that the cardio-hepatic angle becomes obtuse as fluid accumulates in the pericardium. In the past two and a half years, we have found the angle to be acute, both by percussion and by roentgenologic examination (teleroentgenograms and fluoroscopy) except in a few instances in which a right angle was determined (Figs. 1, 2, 3). In no instance was the angle obtuse. The percussion was carried out with the eyes averted or closed; direct percussion, using the second finger, was employed. The shape of the angle has been practically

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unaffected by changing the patient from the recumbent to the erect posture.

The shape of the area of relative cardiac dulness is a matter of considerable interest. It is pear-shaped, except when pericardial adhesions or extra-pericardial lesions interfere with the distention of the sac by the fluid. There is an early increase of the cardiac dulness both to the right, in the third and fourth interspaces, and to the left, beyond the apex. This is more marked when the patient assumes the erect posture, and there is a corresponding change in the fluoroscopic shadow.

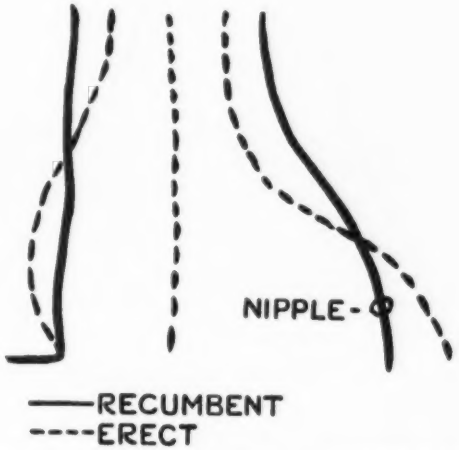


FIG. 2.—Pericarditis with effusion. Relative cardiac dulness in the recumbent (continuous line) and erect (broken line) postures.

Of greater practical importance, in our experience, has been an extension of the relative dulness upward in the first and second interspaces. In this connection, the fact may be recalled that the pericardium extends along the great vessels for a distance of 1½ to 2 inches from their point of origin in the heart; the entire ascending aorta is within the pericardium. An early filling of these cul-de-sacs, as evidenced by an increase in the width of the area of dulness and of the shadow when the patient is recumbent, is one of the most important physical signs of a pericardial effusion. If the dull area and shadow become narrower when the patient is erect, it is indicative of fluid. Thus far, we have encountered this physical sign only in connection with pericardial effusion and have not failed to demonstrate fluid when shifting retromanubrial dulness was found (Fig. 2). Thus, our clinical studies confirm the results obtained experimentally.

The absence of visible pulsation has been noted fluoroscopically repeatedly with large effusions, and has been an aid in the differentiation of this condition and cardiac dilatation. With smaller effusions, a slight pulsation may be observed.

Dulness in the left back near the angle of the scapula, with bronchial breathing, pectoriloquy and bronchophony or egophony, at times with diminished breath sounds and decreased tactile fremitus, noted by many observers, has proved a helpful sign with large effu-

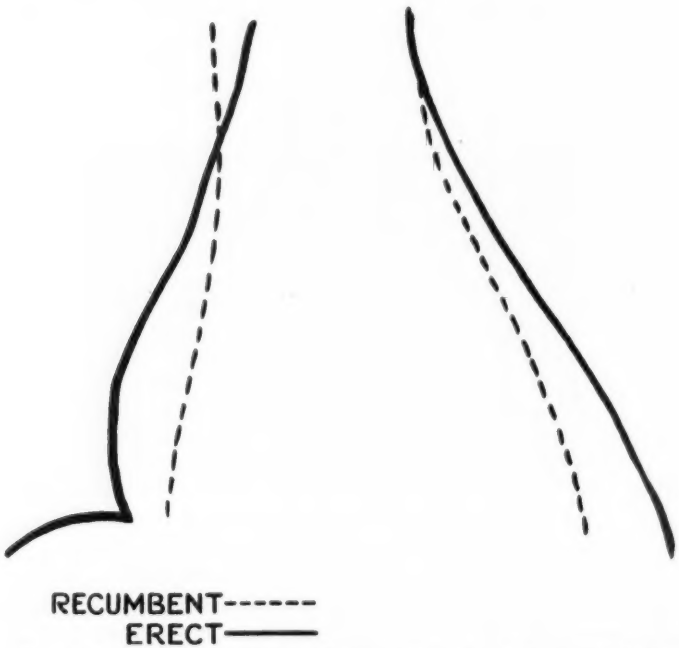


FIG. 3.—Pericarditis with effusion. Fluoroscopic tracing of the cardiac shadow in the recumbent (broken line) and erect (continuous line) postures. (Note. The findings recorded in Figs. 2 and 3 are not from the same patient.)

sions. In one instance, the extent of the dull area was so great that a pleural effusion was diagnosed, but aspiration and subsequent study made it altogether probable that the pericardium had been aspirated.

Conclusions. 1. The cardio-hepatic angle in pericardial effusion is usually an acute angle.

2. The area of relative cardiac dulness in effusion is pyriform and generally extends upward to the first interspace.

3. Widening of the area of dulness and of the shadow in the first

and second interspaces occurs relatively early in effusion and is best determined with the patient in the recumbent posture.

4. Shifting dulness (*i.e.*, a narrowing of the dull area, with a corresponding decrease in width of the shadow over the great vessels when the patient is changed from the recumbent to the erect posture) has proved to be the most reliable physical sign of fluid in the pericardium.

5. Widening of the dull area and of the shadow to right and left above the diaphragm when the patient is erect is found with fluid.

6. There is an absence or marked decrease of visible pulsation in the shadow fluoroscopically in pericardial effusion.

7. Dulness at the angle of the left scapula is often present with a large accumulation of fluid in the pericardium.

STRUCTURAL AND FUNCTIONAL INVOLVEMENT OF THE HEART FOLLOWING ACUTE RESPIRATORY AND OTHER ACUTE INFECTIONS.*

(Second Paper.)

By Walter W. Hamburger, M.D.,

and

Walter S. Priest, Jr., M.D.

Chicago, Illinois.

(From the Cardiographic Laboratory, Michael Reese Hospital, Chicago.)

Three years ago, before the 1920 meeting of the Association of American Physicians, one of us (W. W. H.) presented 6 cases of involvement of the auricle and conduction pathways of the heart following influenza.[1] In this report, it was stated that epidemic influenza causes damage to the cardiac mechanism which may be demonstrated clinically and electrocardiographically, and that this type of infection singles out, to a degree exclusively, the auricle and conduction pathways. The results of these infections were shown to be chronic cases of cardiac involvement, showing arrhythmia and involvement of the auricle, persisting and causing partial invalidism long after the subsidence of the acute infection, lasting from twelve to seventeen months and longer. It occurred to us that it might be desirable to reconsider these 6 cases at this time, to determine if possible the end-results of these acute influenzal infections

* Read at the thirty-eighth meeting of the Association of American Physicians, Atlantic City, May 1, 1923.

[1] Hamburger, W. W.: Involvement of the Auricle and Conduction Pathways of the Heart following Influenza, Am. Jour. Med. Sci., 1920, **160**, 479.

as to the permanency or lack of permanency of such heart involvement. We have attempted to do this and shall make the first part of this report a brief summary of these cases, with the addition of 2 cases which were observed at that time but were not reported. The second part will consist of an analysis of 8 additional cases of involvement of the heart following acute respiratory and other acute infections observed during the past nine months, for the purpose of throwing additional light on this type of cardiac involvement and, if possible, to broaden and crystallize our views on this subject.

Since our original article, one or two noteworthy contributions to this subject have appeared. Paul White,[2] in a general discussion of the heart in infectious disease, considers the effects of influenzal infections to be transient and speaks of them as temporary poisoning. He believes that many symptoms, such as dyspnea, palpitation and precordial pain, are more likely evidence of effort syndrome or irritable heart than of actual structural cardiac involvement. Likewise, Hamilton and Lahey,[3] in an attempt to differentiate hyperthyroidism and heart disease from neurasthenic states, feel that such complaints as breathlessness, tachycardia, heart pain, vasomotor disturbances, etc., are all common to neurasthenia, heart disease and hyperthyroidism. Breathlessness, tachycardia, cyanosis and heart pain do not alone justify the diagnosis of heart disease, as they are found in a variety of conditions, convalescence, fear, fatigue, etc., when the heart is perfectly sound. They emphasize also that neurasthenic states may and frequently do complicate other organic disorders, and that the acute heart disease patient may be disabled by neurasthenic symptoms, complicating, but in no sense directly due to, pathological conditions of the heart. Romberg,[4] in discussing the cardiac findings following influenza, states that acute myocarditis should not be attributed to this condition, and quotes Fahr, who found myocarditis only once among 246 influenza postmortems, although 30 of these cases showed a marked dilatation of the heart. Romberg believes that epidemic influenza produces a functional involvement of the heart muscle, the result of toxic influences, while later certain cardiac symptoms appear, the result of widespread involvement of the entire organism from the infection. He has observed during the epidemic, striking symptoms of arrhythmia, extrasystoles, conduction disturbances, dilatation and muscular mitral insufficiency; during convalescence, evidences of heart weakness, angina-like attacks, here and there arrhythmias or marked bradycardias. The duration of the heart involvement, he found, ranged from a few days or weeks to several years, and mentions one patient,

[2] Am. Jour. Med. Sci., 1922, **163**, 335.
[3] Jour. Am. Med. Assn., 1922, **78**, 1793.
[4] Lehrbuch der Krankheiten des Herzens, 1921, p. 493.

a man, obese, a heavy wine-drinker, nervous, who experienced shortly after an influenzal attack his first heart involvement and died within eighteen months of heart muscle insufficiency. His markedly dilated heart showed, even with the most careful microscopical study, no other demonstrable pathological changes, no evidence of coronary sclerosis, myocarditis, fatty degeneration of the muscle fibers or other changes in the musculature.

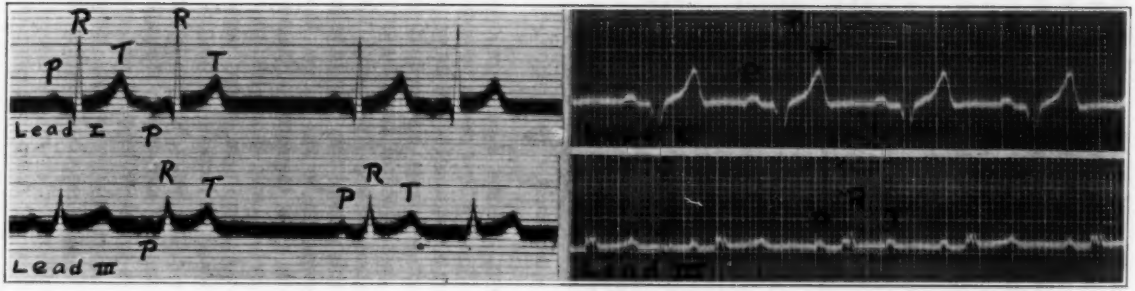
TABLE I.—CASES REPORTED 1920–1921. SUBSEQUENT REPORT.

Case.	Diagnosis (1920).	Present status (1923).
1 S. R.	Postinfluenzal auricular myocarditis.† Pulsus bigeminus. Auricular extrasystoles.	Marked improvement. Only occasionally shortness of breath. Complete disappearance of extrasystoles and bigeminus.
2 Dr. S.	Postinfluenzal myocardial insufficiency.	Not heard from.
3 C. H. W.	Postinfluenzal right ventricular extrasystoles. Ectopic auricular contractions.	No complaints. Occasional extrasystole. EKG shows inverted P_2 and right ventricular extrasystoles.
4 Dr. B.	Acute streptococcus myocarditis,† with auricular extrasystoles and partial A-V block.	Entirely recovered. "No heart lesion that can be detected."
5 Miss E. S.	Acute streptococcus myocarditis,† with partial 3–2 A-V block.	Not heard from.
6 Miss H. N.	Chronic postinfluenzal myocarditis,† with auricular extrasystoles.	Only slight improvement. Frequent attacks of "grippe." Tires easily. Auricular and ventricular extrasystoles.
7 J. M.	Acute postinfectious (streptococcus) myocarditis.† Acute, complete A-V and right bundle branch block.	Entirely recovered. EKG normal.
8 J.C.	Post-infectious (streptococcus, diphtheria) myocarditis,† and nephritis.	Entirely recovered. EKG normal.

† Not based on histological examination.

Cases Reported in 1920. Of the 8 cases reported in 1920, we have been able to trace 6. The first one, a teamster, aged twenty-five years, who, following a severe attack of influenza in April, 1919 was completely incapacitated from his occupation, was listed in our earlier report as a postinfluenzal auricular myocarditis, pulsus bigeminus, auricular extrasystoles. In April, 1920, a year after his influenza infection, this patient was able to take care of a small newsstand to which occupation he was obliged to change, because of his inability to work as a teamster. Examination in April, 1923, four years after his influenza, shows him markedly improved and apparently free from symptoms except occasional shortness of breath on severe effort. Evidences of dilatation of the heart have entirely disappeared, his heart borders being within normal limits. There is no evidence of auricular extrasystoles or bigeminal pulse, which three years ago were brought out, particularly upon exercise. Fig. 1 shows a comparison of his electrocardiographic curves in 1920 and 1923, showing the complete disappearance of the auricular involvement.

This case then should be put down as a complete recovery from a rather widespread involvement of the auricle following influenza within a four-year period.



Series I. Series VI.

FIG. 1.—Case No. I. S. R. (teamster), post-influenzal auricular myocarditis. Series I, pulsus bigeminus, auricular extrasystoles (taken in 1920 during acute infection). Series VI, normal cardiac mechanism, showing absence of extrasystoles and bigeminus (taken April, 1923).

CASE II.—Physician from the South; we have been unable to locate.

CASE III.—Merchant, aged fifty years, with influenza in September, 1918, and recurrence in November, 1918, was diagnosed as a postinfluenzal auricular and ventricular involvement, with right ventricular extrasystoles and ectopic auricular contractions. Examination in February, 1923, four and a half years after his influenza, shows no symptoms or complaints of any description, no dyspnea; an occasional extrasystole still present. Fig. 2 shows his present electrocardiographic curves.

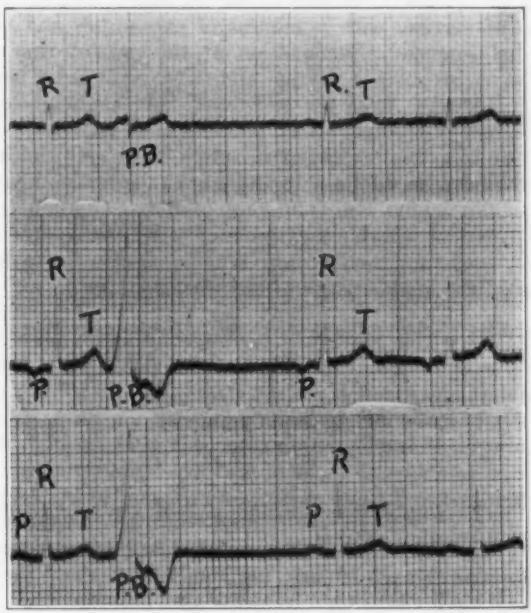


FIG. 2.—Case No. III. C. H. W. (merchant), right ventricular extrasystoles, inversion of P_2 probably indicative of abnormality in the origin and path of the excitation wave in the auricle, inversion of P_3 present in curves three years ago not present now.

CASE IV.—Physician, aged twenty-eight years, who was diagnosed in 1920 as acute streptococcic myocarditis involving particularly the auricle and conduction pathways, reports by letter, March 25, 1923: "I have never felt better in my life. Since leaving the hospital I have refereed football games, have danced and taken more exercise than I have in a number of years, all without discomfort. I have no heart lesion that can be detected. My blood-pressure is 135/80. I am still overweight, but I have

lost 25 pounds since I have been here. I have been able to take out life insurance, being rated up a little on account of my weight. Otherwise I am O.K."

CASE V.—A pupil nurse. This patient, we were unable to locate.

CASE VI.—Stenographer, aged twenty-eight years, who believed her heart trouble followed influenza in October, 1918, and who was diagnosed as chronic postinfluenzal myocarditis with localization in the auricle resulting in auricular extrasystoles has not made as satisfactory a recovery as the others. She has had repeated attacks of "grippe," becomes exhausted easily, has had transitory attacks of vertigo, with numbness of extremities and occasional precordial soreness. Examination at the present time shows a rapid pulse, irregular in rhythm and force; right heart border, 3.5, and left, 10.5 cm., from the midsternal line; slight unclearness of the first tone of the apex which becomes more noticeable on sitting up; 10 to 12 extrasystoles per minute. The electrocardiogram at present, shows, in addition to the original auricular involvement, extrasystoles arising also from the ventricle. One must conclude that this patient still shows evidence of both auricular and ventricular involvement and should continue under observation to determine, if possible, the final outcome of the heart findings.

CASE VII.—This patient, a boy, aged thirteen years, was not included in the original 6 cases, but was published a few months later in the Chicago number of the *Medical Clinics of North America*.[5]

This boy, following an acute follicular tonsillitis, from which pure cultures of hemolytic streptococcus were isolated, developed on the sixth or seventh night of his illness, shortly after midnight, a sudden and complete auriculo-ventricular heart-block with a radial pulse of 28 beats per minute (Fig. 3). At the time, this boy was diagnosed as an acute postinfluenzal (streptococcus) myocarditis, involving particularly the bundle of His and its branches and resulting in transitory complete auriculo-ventricular dissociation and right bundle branch-block. Two weeks after the onset, however, electrocardiograms showed a practically normal cardiac mechanism and a week later he left the hospital apparently entirely recovered. At the present time he is free from complaints of any description and is attending school, preparing himself for a professional career. Physical and electrocardiographic examination are negative.

CASE VIII.—The eighth case, which occurred at about the same time as the others but reported now for the first time, concerns

[5] Hamburger, W. W.: The Administration of Digitalis in the Presence of Certain Acute Infections, Medical Clinics of North America, July, 1921, p. 101.

itself with a young man, aged thirty years, a salesman, who, following an acute streptococcus and diphtheritic sore throat early in 1921, developed weakness, dyspnea on exertion, bradycardia, palpitation and pain. Examination showed a moderate dilatation of his heart, the left heart border being 1 to 1.2 cm. outside of the left nipple. The other findings were negative, except those traceable to a subacute glomerular nephritis, *i. e.*, albumin, granular casts and a blood-pressure of 140/90, slight diminution of his thalein output and increase in the non-protein nitrogen of the blood. Examination on March 19, 1923, shows a slight increase in the degree of left ventricular preponderance, as compared with his findings two years before.

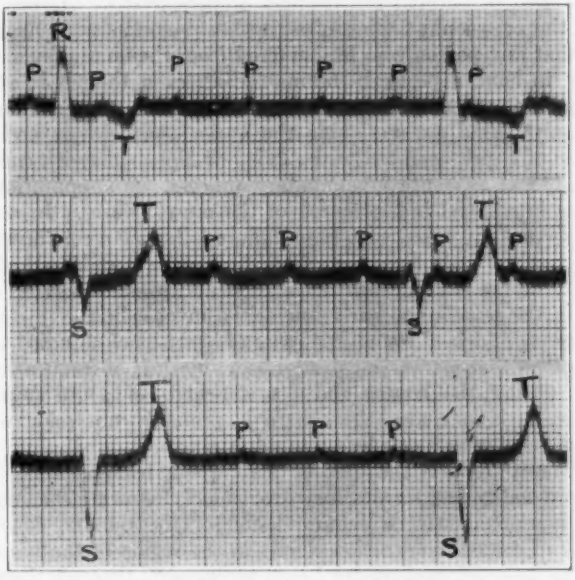


FIG. 3.—Case No. VII. J. M., school boy, aged thirteen years, acute infectious (streptococcus) myocarditis with complete A–V and right bundle branch block. Leads I, II, III taken October 27, 1920, on entering hospital. First published Medical Clinics North America, July, 1921.

Summarizing the results of these 8 cases, 5 patients present no complaints, particularly no cardiac complaints, and have apparently entirely recovered from the effects of their influenzal involvement. One patient still shows evidence of auricular and ventricular disease and 2 patients cannot be traced. One must conclude, therefore, with White, Romberg and others, at least so far as this small series is concerned, that the effects of influenza are

transitory in character, that, although widespread involvement of the heart may be demonstrated at the time of or shortly following the acute infection, within a four-year period these effects have completely disappeared. From the findings of these cases, it is extremely difficult, however, to conclude finally as to the exact nature of the involvement following influenza in terms of pathological anatomy and pathological physiology. One is not quite satisfied with the statement of an acute poisoning, but without experimental or histological findings it is impossible to say whether the effects observed might be due to cloudy swelling, edema, acute myocarditis, acute neuritis of the vagus or other pathological involvement. In this connection, White speaks of a transient heart-block occurring in rheumatic fever in hearts which do not show signs of pathological changes or pericarditis. He concludes that the occasional finding of acute heart-block should make one feel that any person who has suffered from rheumatic fever is not likely to have a perfectly normal heart, even though it appears normal to auscultation and percussion. Cowan, Fleming and Kennedy[6] found, on sectioning the auriculo-ventricular node and bundle of a girl, aged ten years, dying of diphtheria with complete heart-block, an acute inflammatory process, with separation and diffuse interstitial inflammation of the muscle fibers. In a male, aged twenty-six years, with heart failure following a cold and death from cerebral embolism, section of the heart showed marked congestion of the auriculo-ventricular node, with small foci of round cells in the bundle and early interstitial myocarditis.

Magnus Alsleben[7] found in 4 cases of heart-block (studied microscopically) that a transient partial heart-block is of frequent occurrence during the course and convalescence of acute infectious disease, and concludes that there is probably no lesion of the bundle itself, the block being vagal in origin.

Gerhardt[8] reports the case of man dying from typhoid fever, who previously had a transitory heart-block following rheumatism. Examination showed a definite lesion of the bundle, consisting chiefly of cellular infiltration chiefly in the region of the vessels.

Allen[9] believes, and quotes Lewis in support, that all transitory blocks are on the basis of organic lesions of the bundle, rather than on vagus effects, and concludes that such evidence of involvement of the bundle by partial or transitory block is certain evidence of myocardial change.

As we stated in the 1920 report, we have had no opportunity for microscopical study of hearts following influenza and showing clinical and electrocardiographic evidence of involvement of the

[6] Heart Block and Nodal Rhythm in Acute Infections, Lancet, 1912, **1**, 277.
[7] Ztschr. f. klin. Med., 1910, **69**, 82.
[8] Deutsch. Arch. f. klin. Med., 1912, **106**, 462.
[9] British Med. Jour., 1913, **1**, 484.

conduction pathways, so that direct proof of this point cannot be offered in this series of cases. However, from our experience and a study of the literature, we incline to the view that partial or complete block is due to organic changes in the bundle rather than to vagal influences, although conceivably both might be present. The fact that these changes may be transitory does not itself speak against this view.

Also, our experience, that the majority of these cases cleared up within a three- or four-year period, does not speak against this conclusion. Either the scarring of the bundle, the theoretical result of such involvement, could be of such degree which would not affect the conduction pathways, or the cloudy swelling, edema, hemorrhage, cellular infiltration and acute interstitial inflammation which formed the structural basis of the detected temporary functional defect might be entirely recovered from. Whether or not involvement at one time predisposes to a repetition at a later date, we have no experience which is relative.

New Cases, 1923. The 8 new cases observed during the past nine months, we believe, show evidence of both structural and functional involvement of the heart, the relative degree of each factor varying in the individual case. We have, therefore, divided these 8 new cases into 2 groups of 4 each; the first with predominant structural involvement, in which definite and unmistakable evidence of organic heart involvement can be demonstrated with a lesser degree of functional symptoms; the second, in which the functional involvement predominates, while definite structural disease is either slight or questionable. The majority of these cases have followed acute influenzal infections or some complication thereof.

TABLE II.—CASES SHOWING PREDOMINANCE OF STRUCTURAL HEART INVOLVEMENT.

Case.	Etiological diagnosis.	Structural diagnosis.	Functional diagnosis.	EKG diagnosis.	B.M.R.
No. 9 Mrs. W.	Influenza; pneumonia	Subacute† myocarditis	Early heart failure	Partial A-V block	7.2% plus.
No. 10 Mrs. L.	Influenza; pneumonia; acute arthritis; empyema. * Measles; diphtheria; epidemic influenza, 1919	Subacute† myocarditis and endocarditis; mitral stenosis, aortic insufficiency	Moderately advanced heart failure	Partial A-V block; right bundle branch block	20.0% plus.
No. 11 Mrs. G.	Influenza; pneumonia * Diphtheria 7; pneumonia 1918	Chronic myocarditis† and endocarditis; mitral stenosis and regurgitation	Moderately advanced.	Sinus rhythm	20.1% minus.
No. 12 Mr. P.	Peritonsillar abscess (streptococcus) * Pneumonia 9 years ago	Subacute endocarditis; mitral insufficiency; subacute glomerular nephritis	Moderately advanced heart failure	Sinus rhythm	12.8% plus.

* Acute infections above, previous infectious diseases below the line.
† Not confirmed by histological examination.

PREDOMINANT STRUCTURAL INVOLVEMENT. The first patient of the "structural group" (Case IX) is a woman, aged thirty years, who developed, in October, 1922, a diffuse bronchopneumonia following influenza, during the course of which she showed a rapid,

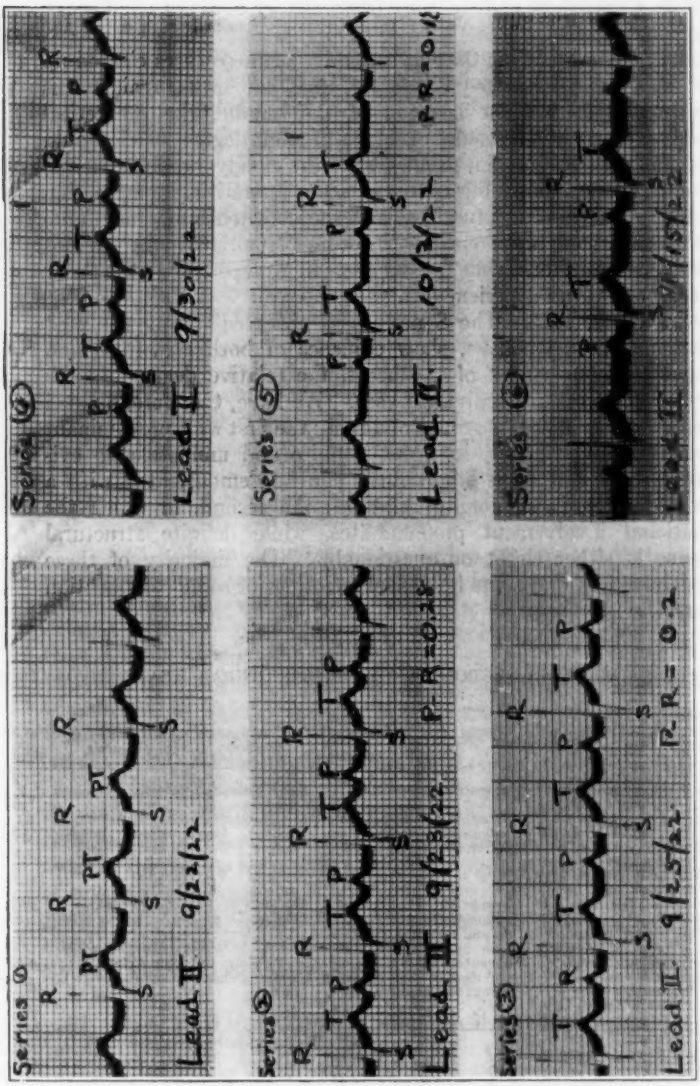


FIG. 4.—Case No. IX. Mrs. S. W., aged thirty years, housewife, influenzal bronchopneumonia, postinfectious subacute myocarditis with partial A–V heart block. Series of six electrocardiograms (Lead II) taken at varying intervals during course of infection (six months), from first series taken at the height of infection to last showing restoration of normal cardiac mechanism.

irregular pulse which proved to be a partial auriculo-ventricular block (Fig. 4). The discharge diagnosis was postinfluenzal bronchopneumonia, postinfluenzal subacute myocarditis with partial auriculo-ventricular heart-block. The heart was moderately enlarged to the left; the blood-pressure, 102/78.

This patient is still under observation. Her heart is now rapid, but regular and enlarged to the left. She still complains of marked dyspnea on only slight walking, precordial pain, has a very limited cardiac reserve; becomes quickly exhausted on slight effort and is

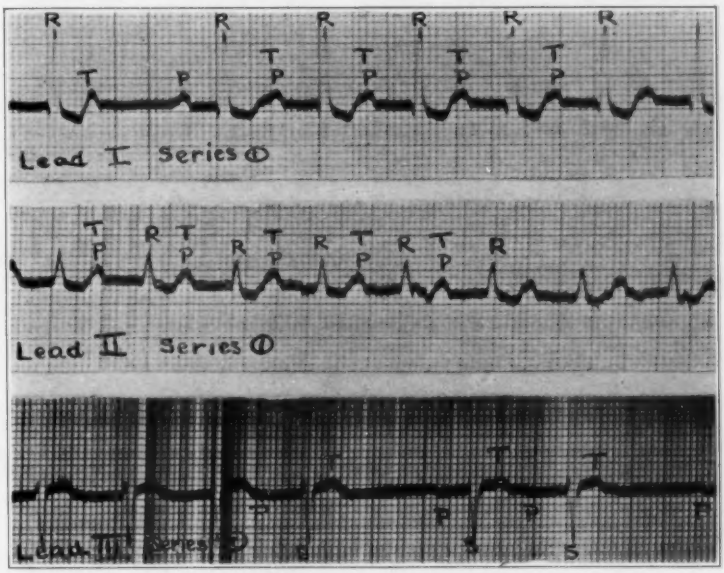


FIG. 5.—Case No. X. Mrs. E. L., aged twenty-six years, housewife, combined rheumatic and postinfluenzal heart disease, influenzal bronchopneumonia with empyema; postinfectious subacute myocarditis with partial A–V heart block, and right bundle branch block; subacute mitral and aortic endocarditis with mitral stenosis and aortic insufficiency. Tracing made September 13, 1922 (Series I), two months after onset of rheumatic infection and one month after onset of acute lung infection.

pale, gray looking and cyanotic. She had had no acute infectious diseases prior to her pneumonia. She is nervous, depressed, worries a great deal regarding her condition and runs an occasional slight afternoon temperature. We consider the partial auriculo-ventricular block, dyspnea, cyanosis and enlargement of the heart, and easy exhaustion, due to structural disease; the other symptoms, functional.

The second patient (Case X), a young married woman, aged twenty-six years, developed six weeks prior to her admission an

acute infectious arthritis and three weeks later an acute pleuritis with bronchopneumonia and empyema. She had measles, mumps and diphtheria as a child and influenza in 1919. The completed diagnosis was acute infectious arthritis, influenzal bronchopneumonia and empyema, postinfectious subacute endocarditis and myocarditis, with aortic insufficiency and mitral stenosis, partial auriculo-ventricular and bundle branch-block (Fig. 5). She had

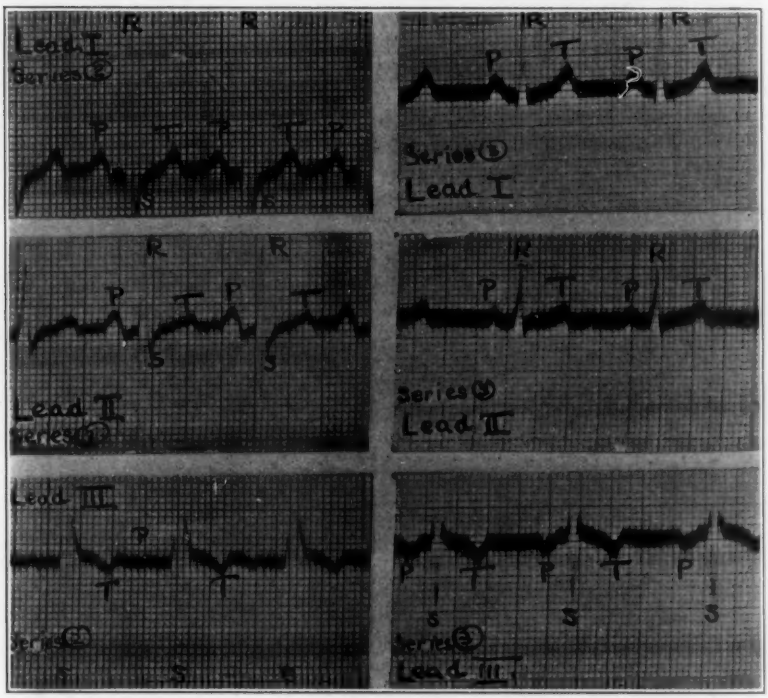


FIG. 6.—Case No. X. Mrs. E. L. Series (II) and (III), postinfectious A–V and bundle branch block; Series (II) made November 18, 1922, two months after Series (I); Series (III) made February 27, 1923; five months after Series (I). Both show disappearance of A–V and intraventricular block and gradual return to normal cardiac mechanism.

some evidence of thyroid involvement, her basal metabolism rate being 20 per cent plus, blood-pressure of 142/80 and pulse 112 (Fig. 6).

She apparently has completely recovered and is able to be out of bed and perform her household duties with no evidence at the present time of heart failure. This patient was extremely ill for many weeks; lost between 40 and 50 pounds in weight; was at times deeply cyanotic with orthopnea, with enlarged tender liver, etc.;

at all times frightened, depressed, apprehensive, complaining of insomnia, anorexia, etc. Her breathing and pulse were at times extremely rapid. She needed many months to regain her equilibrium, cardiac reserve and ability to walk about. We feel the mitral and aortic disease, conduction path involvement, dyspnea, heart dilatation and cyanosis are due to structural disease; many of the other findings, either functional (effort syndrome) or related to the thyroid involvement.

The third patient (Case XI), a married woman, aged thirty-five years, has early, slight heart muscle failure with mitral stenosis and regurgitation, apparently the result of epidemic influenza and pneumonia in 1918. Her blood-pressure is 120/80. When first seen she had limited response to effort, edema of ankles, cyanosis, decreased urinary output. On rest in bed and moderate amounts of digitalis, she apparently has completely recovered. Her findings are all structural in origin except the attacks of simple tachycardia, anxiety, depression, etc., which we interpret as being of psychogenic character.

The fourth patient (Case XII), a man, aged thirty-seven years, who, following a peritonsillar abscess in which hemolytic streptococcus was found, developed swelling of the feet and legs, decreased urinary output, pallor, dyspnea, rapid pulse and weakness. Blood-pressure varied from 140/100 to 157/92. His urine showed occasional blood, a large number of casts and considerable albumin. He had had pneumonia nine years ago. His right heart border was 3 cm. and the left 9 cm. from the mid-sternal line, with a soft presystolic and systolic murmur at the apex. He was diagnosed post-infectious heart disease, subacute mitral endocarditis with mitral insufficiency and stenosis and moderately advanced heart failure. His pulse at all times has been extremely rapid.

The electrocardiogram showed an inversion of the T-wave in the first lead. He is still under observation and is dyspneic on effort and is pale. The majority of his findings, we believe, are on an organic basis.

SUMMARY. These 4 cases, we believe, show that, as a result of these acute infections, various portions of the heart, endocardium and myocardium or both are involved, and that, although marked recovery has occurred during these early months, at least in 2 of them evidence of heart failure still exists. We conclude that acute influenzal infections cause structural damage to the heart, even as the older, better recognized infections, acute rheumatic fever, diphtheria, etc. We believe that following these acute respiratory infections, the development of valve murmurs (particularly diastolic), cyanosis, dyspnea, orthopnea, diminished urinary output, enlarged tender liver, auriculo-ventricular or bundle branch-block, enlargement of the heart to percussion, are clear evidences of organic disease. The fact that under adequate treatment most

or all of these findings are relieved, does not, we believe, speak against this view. The rather constant association of nervousness, depression, anxiety, insomnia, anorexia, occasional tremor, tachycardia, breathlessness, precordial pain, easy fatigue, are functional or thyroid in origin. Of particular interest, and emphasized here for the first time as far as we know, is the association of these two groups of findings in these patients suffering from the results of these acute respiratory infections.

PREDOMINANT FUNCTIONAL INVOLVEMENT. The following 4 cases show evidences of marked functional and questionable structural involvement of the heart.

TABLE III.—CASES SHOWING PREDOMINANCE OF FUNCTIONAL HEART INVOLVEMENT.

Case.	Etiological diagnosis.	Structural diagnosis.	Functional diagnosis.	EKG diagnosis.	B.M.R.	Neurological diagnosis.
No. 13 Mrs. S.	Influenza (epidemic 1918) *	Subacute myocarditis†	Early heart failure (?) effort syndrome	Low voltage; inversion and notching R3	21.7% minus	Anxiety state.
	Diphtheria 9; chorea 13. Diarrhea with fever 3 and one and a half years ago					
No. 14 Mrs. F.	Puerperal infection; Cesarean section. *	Subacute† myocarditis	Early heart failure (?) effort syndrome	Low voltage; inversion and notching R3	14.9% plus	Major hysteria.
	Diphtheria 5; typhoid 15. Epidemic influenza 1918; acute inflammatory rheumatism 1918					
No. 15 Mrs. R.	Epidemic influenza (1918)	.....	Effort syndrome	Paroxysmal tachycardia	1.4% minus	Anxiety state.
No. 16 Mrs. B.	Epidemic influenza (1918) *	Subacute† myocarditis	Thyrotoxic heart	Low voltage; inversion and notching R3	17.1% plus	Hyperthyroidism.
	Scarlet fever 4; typhoid 11	Subacute thyroiditis				

* Acute infections above, previous infectious diseases below the line.
† Not controlled by histological examination. Autopsy findings in similar cases show only dilatation.

The first patient (Case XIII), a married woman, aged thirty-five years, complains of occasional palpitation of the heart, attacks of pain under the left breast of three years' duration, the first attack occurring following acute diarrhea and fever three years ago. She had diphtheria at nine and chorea at thirteen years. Examination is essentially negative. Blood-pressure is 112/60 and basal metabolism 21.7 per cent below normal. She was diagnosed as postinfectious myocarditis (?) and anxiety state. The electrocardiogram showed an extremely low voltage in the third lead, with inversion of the initial ventricular complexes, a frequent finding in these postinfectious functional cases. Under preliminary rest in bed, later graded exercises, reassurance regarding her condition, alternating thyroid and bromide medication, she has made satisfactory progress.

The second patient (Case XIV), a married woman, aged twenty-nine years, complained of dyspnea, extreme nervousness and continuous temperature since the birth of her third baby five months

previous. She had diphtheria at five, typhoid at fifteen years, epidemic influenza and pneumonia in 1918 and acute infectious arthritis in 1918. She is a large, obese, pale and unhealthy looking woman. Her basal metabolic rate is 14.9 per cent above normal. The electrocardiogram is negative, except for the same low voltage and inversion of the QRS group, as in the previous case. She was diagnosed as postpuerperal myocarditis, major hysteria and subacute hyperthyroidism. She is somewhat improved at the present time.

The third patient (Case XV), a young married woman, aged thirty-five years, suffered severe, sudden, acute attacks of tachycardia, which we believe were true paroxysmal tachycardia, the first attack occurring four years ago following epidemic influenza. She has had no other acute infectious diseases. Examination is essentially negative, except that she is extremely thin and poorly nourished. The electrocardiogram is negative, except for low voltage in the third lead. Although she is improved, any severe emotional display is apt to be followed by an abrupt onset of her tachycardia.

The fourth patient (Case XVI), a married woman, aged thirty years, believes she has not been well since influenza in 1918 and again a "grippe" attack in September, 1922. She complained of an extremely rapid pulse, with failure to gain weight. She has no dyspnea. Examination shows an enlargement of the left thyroid lobe and a metabolic rate of 17.1 per cent +; pulse, 118, and blood-pressure, 144/88. She was diagnosed as postinfluenzal subacute myocarditis and thyroiditis with hyperthyroidism. Under complete rest in bed, bromides and occasional small amounts of digitalis, she has made a satisfactory gain. She had scarlet fever at four and typhoid at eleven years.

These 4 cases may be discussed together. We conclude that in view of the findings of palpitation, precordial pain, periodic attacks of nervousness, exacerbation of cardiac symptoms following emotional excitement, persistent tachycardia and breathlessness, presence of depression and anxiety states that this type of case following epidemic influenza is largely functional in origin of the group variously called irritable heart, effort syndrome, neurocirculatory asthenia. The fact, however, that they failed to recover entirely under treatment directed to such functional disorder, but have recovered following prolonged rest in bed and digitalis, in addition to adequate psychological management, justifies the conclusion that a minor portion of their complaints are of structural origin.

Summarizing the significant facts in these two groups of cases we find the following: They all show the development of their cardiac symptoms following acute respiratory infections (influenza). The significance and interpretation of these cardiac symptoms are,

of two types, one structural and the other functional, the relative degree of each varying in the individual case, in 4 being predominantly structural, in 4 functional. The majority of these cases have secured either complete recovery or marked improvement, the result being attained by a combination of treatment directed toward both structural and functional disease. We believe, therefore, that in the evaluation of this type of cardiac trouble following epidemic influenza it is of service to consider in each case the possibility of such dual disease, as we have found with such consideration the effects of treatment are markedly enhanced. In other words, instead of attempting definitely to separate organic from non-organic findings, this series of cases presents evidence representing a dual involvement. We desire to point out this possibility in each instance of postinfluenzal cardiac disease.

Considering these 16 cases as a whole, our first group of 8 cases of three years ago and the present series of 8 cases observed this past year, we reach the following conclusions: Acute respiratory infections (influenza) may and frequently do produce cardiac symptoms. These symptoms are often caused by both structural and functional involvement of the heart. Structural involvement is recognized by delayed conduction time, partial, complete or bundle branch-block, enlargement (dilatation) of the heart, endocardial murmurs and signs of early heart failure. Functional involvement is recognized by palpitation, precordial pain, fatigue, weakness, nervousness, anxiety, depression, cyanosis, dyspnea, pallor, tachycardia. These two groups of symptoms may and frequently do coexist in the same patient, and it is this coexistence of structural and functional involvement which we wish to especially emphasize. Structural involvement is often evident at first, may be entirely overlooked and is often extremely transitory. Functional involvement appears later, often dominates the clinical picture and usually requires a longer period for relief.

Conclusions. 1. A reconsideration of 8 cases of postinfluenzal cardiac disease, first observed and reported in 1920–1921, shows 5 completely recovered, 2 not traceable and 1 unimproved.

2. Eight new cases of cardiac involvement following acute respiratory infection observed during the past nine months present evidence of both structural and functional involvement, half predominant structural, half functional.

3. Diastolic murmurs, enlargement of the heart to the left, swelling and tenderness of the liver, edema of ankles and diminished urinary output, auriculo-ventricular and bundle branch-block serve as criteria of structural disease; palpitation, tachycardia, precordial pain, nervousness, depression and anxiety states are suggestive of functional involvement; breathlessness, cyanosis, weakness, exhaustion and fatigue are of indeterminate interpretation and significance.

4. The possibility of coexistent structural and functional disease should be borne in mind in a survey of any postinfectious heart patient. Treatment directed toward amelioration of both types of symptoms offers not only the most favorable chance of recovery, but may be of differential diagnostic value.

5. Delayed conduction time, partial, complete or bundle branch-block occurring at the height of an acute respiratory infection may be interpreted as structural heart involvement. The fact that such findings may be based upon extremely slight or negative histological findings and are transitory in character does not of itself speak against this view.

6. It is desired especially to emphasize the coexistence of structural and functional involvement of the heart (following influenza) in the same patient. Structural involvement is often evident at first, may be entirely overlooked and is often extremely transitory. Functional involvement appears later, often dominates the clinical picture and usually requires a longer time for relief.

DETAILS IN THE TREATMENT OF HAY-FEVER, ASTHMA, AND OTHER MANIFESTATIONS OF ALLERGY.*

By W. W. Duke, M.D.

KANSAS CITY, MISSOURI.

The development in our knowledge of the subject hypersensitiveness, its diagnosis, and treatment, marks an important advance in the theory and practice of medicine. Through acquaintance with this sphere of work, we are now able to understand and relieve many kinds of illness which in previous years were looked upon as obscure in origin, and not amenable to treatment.

Illnesses caused by hypersensitiveness to foreign substances, can be treated along five different lines, namely: Avoidance or removal of the specific cause of illness; avoidance or removal of contributory causes; specific protein treatment; non-specific protein treatment; symptomatic treatment.

Each of these measures is important. The choice depends upon the severity of the illness, upon the degree of hypersensitiveness, and upon the nature of the substance to which the patient is hypersensitive. In the majority of cases, two or more of the above measures can be used to advantage. The simplest method is best when the simplest can be used—namely, avoidance or removal of the specific cause of illness. However, removal of the specific cause is often difficult or impossible. This is true in the case of

* Read in brief before the Chicago Medical Society, February 28, 1923.

sensitiveness to the common pollens, to common foodstuffs (milk, eggs, and wheat), to products originating in the body which cannot be removed, and to substances which cannot be discovered by means at our disposal. In these instances, one or more of the latter four measures must be chosen.

Removal of Cause. Having ascertained the fact that a patient is sensitive to a certain substance, it is important to know whether the clinical symptoms occur as a result of direct contact between the substance and the affected tissues, or occur as part of a general reaction. For example, in the case of asthma caused by sensitiveness to wheat, it is important to know whether the respiratory symptoms result from direct contact between the mucous membrane of the bronchial tubes and wheat flour inhaled, or whether they occur as part of a general reaction due to the ingestion of wheat bread. In the former case, bread can be eaten with impunity and the patient, to be relieved, needs only to avoid contact with wheat flour. In the latter case it may be necessary to remove wheat from the diet.

It is, furthermore, important to know whether an individual is sensitive to a given substance as encountered in its natural state only, or whether he is also sensitive to the substance after it has been cooked. For example, an individual sensitive to lactalbumen, is made ill by raw milk, but tolerates unlimited amounts of cooked milk. In the case of sensitiveness to egg white, an individual can tolerate cooked egg. In sensitiveness to ovomucoid, however, he may be made ill by either raw or cooked egg.

The ocular, nasal, and bronchial symptoms, and eczema confined to the hands, face, and ankles are in the majority of cases attributable to direct contact between the mucous membrane or skin and the substance to which it is sensitive.

Urticaria, angioneurotic edema, generalized dermatitis, bladder allergy, hypotension, and neurological manifestations usually occur as part of a general reaction. Air carried allergens are rarely absorbed in sufficient quantity to give rise to these general symptoms, although this does actually occur occasionally. As an example, I may mention a case of autumnal hay-fever in which the dominating symptoms were neurological.

Gastro-intestinal manifestations may result from local contact of the mucous membrane with a food or may occur as readily as part of a general reaction after absorption of an offending food product.

As a rule, a symptom such as asthma, occurring as part of a general reaction, is frequently associated with other manifestations of general reaction such as hives, angioneurotic edema, etc. This is not true of the same symptom, asthma, when it occurs as a local reaction, that is as a result of local contact of the bronchial mucous membrane with air-carried substances. Bearing in mind this gen-

eral rule, it is often possible to surmise correctly that a symptom, such as asthma, hay-fever, or eczema, is due to exposure to some air-carried substances, or to a food which has been eaten, or to some product which has been elaborated in the body. A knowledge of this fact is often useful in the attempt to relieve the patient.

POLLEN. Pollen can usually be avoided by a change in geographical situation. In the case of sensitiveness to light air-carried pollen of the common weeds which pollenate over a long season, complete avoidance can hardly be accomplished otherwise. Pollen can be avoided in sufficient degree to give relief in mild cases by removal of the common weeds of the neighborhood, by having the patient confine his activities to downtown districts, by avoidance of trips in the country, by having him live and work on the upper floors of office buildings or hotels, and by having him keep the windows closed. This often gives partial or complete relief in mild cases, except on windy days when the air is filled with pollen even at the top of high buildings. Scheppegrell's ingenious experiments have shown the marked effect of a strong wind on the distribution of pollen in the air at different heights.

In the case of sensitiveness to rare pollens such as choreopsis, relief can easily be obtained by avoidance of districts in which the flowers grow profusely, or by having them removed from the immediate vicinity.

PRODUCTS OF VEGETATION OTHER THAN POLLEN. Products of vegetation other than pollen, can usually be avoided easily if the source of the illness is recognized. Orris root is worthy of especial mention since this product is so widely used in the manufacture of perfumes, flavoring extracts, toilet articles of all sorts, including tooth paste, face powder, and soap.

In the case of sensitiveness to the stalk or leaf of plants, such as clover or straw, the offending substance, as a rule, can be avoided sufficiently to relieve symptoms if the patient is aware of the source of his trouble. Clover, on account of its profuse growth, is difficult to avoid entirely; but, according to our experience, the degree of sensitiveness is not extreme in grade so that its complete avoidance is not necessary.

The essential oils and other products of plant life such as turpentine, cedar oil, the oils used in perfumes and flavoring extracts, also the products derived from coal, such as benzol and those derived from crude oil, such as gasoline, can usually be avoided easily if recognized as a source of illness.

FOOD. The symptoms of food idiosyncrasy usually occur as part of a general reaction to a food or a split product. In the case of sensitiveness to uncommon articles of diet, such as tomato, onion, and cabbage, avoidance is simple. When a patient is sensitive to articles used so commonly in cooking, as milk, eggs, or wheat, avoidance is difficult, especially if he is sensitive to the

cooked as well as the raw product. It is rarely advisable to attempt specific treatment in a case unless sensitive to cooked milk, egg, or wheat.

Animal Products. It is rarely advisable to treat specifically for sensitiveness to animal dander such as horse, cat, or dog, since the animals and their pelts can usually be avoided. In several cases of sensitiveness to wool (all eczemas) observed by the writer, the symptoms were not severe and were relieved through the use of cotton clothing between the skin and woolen garments.

Walker has obtained splendid results in increasing tolerance for animal dander, by subcutaneous inoculations with dander extracts. He does not recommend this treatment when avoidance is possible. In sensitiveness to feathers, such as goose, duck, or chicken, relief can be obtained by the use of floss pillows. This type of sensitiveness is rather rare in my experience.

Drugs. When individuals are sensitive to drugs, such as iodoform, formalin, novocaine, morphine, aspirin, etc., relief of symptoms can be obtained if the cause is discovered. One is occasionally sensitive to an impurity in a drug. This is important in the case of drugs so useful as acetyl salicylate and arsphenamine for an individual sensitive to one preparation of a drug can often tolerate other preparations.

House Dust. House dust is worthy of especial mention since it is frequently responsible for house asthma, the importance of which has been especially emphasized by Cooke. Relief can often be obtained by the removal of certain articles of furniture, upholstery, rugs, disinfectants, cleaning fluids, glue, etc.

In one interesting case, observed by the writer, sensitiveness was traced to wood smoke. It was found the patient could live comfortably only in steam heated apartments and that she invariably had severe asthma in houses where open fires or furnaces were used. She was so affected even during the summer months when the furnaces were not in use.

Smoke. Individuals sensitive to smoke can frequently obtain relief by slight change in environment. One patient who had asthma due apparently to gasoline smoke, could invariably obtain relief by moving to a different part of a hotel in which he lived. The room which he occupied at the time of his illness was situated directly over the garage. Individuals sensitive to coal smoke should be cautioned against long railroad trips, since in this position they are frequently exposed intensely to smoke and may suffer a severe exacerbation of their illness.

Bacteria. Definite symptoms of allergy often accompany acute infectious diseases, such as rheumatic fever and scarlet fever. These manifestations can be treated best symptomatically since they often disappear spontaneously after the acute illness has subsided. Individuals sensitive to products elaborated in chronic

foci of infection, should be treated by removal of such foci. When the focus cannot be reached, however, treatment with vaccines is justifiable. According to Walker and Rackemann, this method of treatment frequently yields beneficial results.

THERAPEUTIC SERA. In demonstrated hypersensitiveness to horse serum, the therapeutic use of horse serum is dangerous even in very small doses and should not be used. Antitoxins of sources other than horse should be provided for patients of this type. Patients sensitive to horse dander are not necessarily sensitive to horse serum. If there is any question whatever, intracutaneous tests should be made before serum is administered.

BLOOD TRANSFUSION. I have observed 2 cases of collapse at the beginning of blood transfusion, both relieved by the hasty use of adrenalin. In each case the bloods had been tested with great care for compatibility, so far as agglutinins were concerned. Upon inquiring into the cause of the collapses, it was found in 1 case that the patient came from a hypersensitive family, had suffered from asthma due to milk, and gave positive intracutaneous tests with lactalbumen. The second patient was sensitive to tomato and cabbage. In each case the donor had eaten foods to which the patients were sensitive and no such results followed the use of other donors. The reactions were believed to be due directly to sensitiveness on the part of the patients to foods eaten by the donors. The statement, while seemingly fantastic, appeared to us actually very real, and would seem analogous to the eczema of breast-fed babies caused by sensitiveness of the infant to certain foods eaten by the mother.

LIGHT. One patient observed by the writer was specifically sensitive to violet light or the violet rays of white light; or better stated, sensitive to some product elaborated in the tissues under the influence of light. She would become ill invariably if exposed a few moments to sunlight. Exposure of the skin to either sunlight or light of a nitrogen lamp or light filtered through violet glass would give rise to erythema in less than three minutes and to a wheal covering the entire area exposed in five and a half minutes. Roentgen-ray, actinic-ray, heat, colored light (except violet) and several kinds of mechanical and chemical irritants produced no noticeable effect. She was completely well when protected from light. Her skin was rendered tolerant in one locality by repeated exposure to light so that she could tolerate a ten-minute exposure in this locality with apparently no change in the skin. After several weeks the tolerance gained in this way was lost. Our complete study of this interesting case has been reported in another communication.

MULTIPLE SENSITIZATION. Patients sensitive to a number of substances may tolerate some of them if the others are carefully avoided. For example, many patients with pollen hay-fever give positive

skin tests to vegetables, fruits, or grains and actually obtain partial relief of hay-fever by avoidance of the food products to which they give positive tests. These substances may have no untoward effect except during the pollen season. One patient with hay-fever and eczema was found sensitive, among other things, to a certain silk dress. An extract from the dress gave an intensely positive cutaneous test. It was observed, however, that when her illness was relatively mild due to the avoidance of other substances which made her ill, she could wear the silk dress with impunity. At other times, however, when she was suffering markedly with hay-fever, and dermatitis, the wearing of the dress invariably caused itching and an increase in the rash and asthma.

SUMMARY. To recapitulate, the avoidance or removal of the specific cause of reaction is the simplest and surest method of treatment when this can be accomplished. It is only in cases where the specific cause is not discovered or cannot be removed that the measures to be described subsequently need be resorted to.

Removal of Contributory Causes. Very frequently it is impossible to discover the specific substance primarily responsible for the manifestations of allergy. In this case, removal of certain contributory causes may relieve the patient partly or completely.

PHYSICAL FACTORS. Physical factors which definitely add to the symptoms of reaction and often determine their site of localization, are divided by Walker, into mechanical, chemical, odorific, and thermal. To this may be added reflexes and functional activity as common contributors. The untoward effect of these factors has been mentioned by many observers and is noticed by a large proportion of sensitive patients. For example, patients subject to urticaria are frequently relieved to a marked extent by the removal of agents which irritate the skin mechanically; by the avoidance of agents which cause increased activity of the glands (sweating); by protection of the skin from heat or cold and by the avoidance of irritating lotions.

Similarly, patients who have dyspepsia and abdominal pain as a result of alimentary reaction, can often obtain partial relief by the avoidance of foods, such as nuts, which irritate mechanically; by the avoidance of substances such as coffee, and alcohol, which stimulate functional activity; by the avoidance of condiments, such as mustard and pepper which irritate chemically; and by the removal of the source of abnormal reflexes, such as a diseased appendix or gall-bladder.

Likewise, patients who have asthma are often relieved to a marked extent by the avoidance of dust, irritating vapors, the odor of flowers, essential oils, or perfumes; by living in a dry climate; and finally, by the correction of pathological defects in the nose or gastro-intestinal tract or other localities which give rise to pathological reflexes.

Pathological Factors. Patients who are ill with symptoms of reaction (especially general reaction) are occasionally relieved completely by another disease. I have observed 3 cases of asthma who apparently were permanently relieved by severe infectious diseases—erysipelas in 2 cases and scarlet fever in 1. As a rule, however, additional illnesses make the symptoms worse. Frequently asthma starts after an acute infection, an operation, especially intranasal operations, or other illnesses. Asthma is almost always made worse by infections in the respiratory tract. Many individuals subject to asthma have asthma only during and for several weeks following attacks of acute rhinitis, bronchitis, or sinus infection. Alimentary reactions are usually made worse by ulcer, gall-bladder disease, or chronic appendicitis. Very often partial or complete relief can be obtained by attention to these conditions.

Dysfunction in the glands of internal secretion, which is rather frequently noticed (in cases of general reaction) often adds to the severity of the illness, and treatment of these conditions may give partial relief.

Summary of Contributory Causes. To recapitulate, when one fails in his effort to find or remove the specific cause of illness, frequently his only recourse lies in paying attention to other abnormalities and illnesses with which a person may be afflicted. A serious, careful effort in this line often gives relief, which can be obtained in no other way.

Specific Protein Treatment. In view of our knowledge of the tolerance which can be developed in patients or animals for living bacteria by subcutaneous inoculation with their products, and in view of the fact that hypersensitiveness to serum in animals can be completely removed by inoculations with serum, it has been quite natural that many investigators working both jointly and independently should have tried this method of treatment on human beings sensitive to pollen and other bodies, not of bacterial origin. These researches have been described under the terms anaphylaxis, protein sensitization, allergy, specific hypersensitiveness, etc.

It is good fortune that tolerance for foreign substances can frequently be developed in this way in sensitive patients, and it is surprising that statistics published by different writers using different plans in therapy agree in the essentials concerning the results which can be obtained. For the many names and researches responsible for the development of this line of knowledge, the reader is referred to the authors mentioned in the bibliography.

Pollen Treatment. The practical development of this line has been due to the efforts of a number of investigators, among whom may be mentioned, Curtis, Dunbar, Noon, Freeman, Koessler, Lowdermilk, Rackemann, Walker, Cooke, Scheppegrell, Goodale,

and others. The method generally employed lies in the use of increasing doses of pollen extract given subcutaneously at varying intervals of time. An increase in tolerance for pollen is the result in the majority of cases with partial or complete relief of symptoms. The writer has used this method each year since 1915, trying different plans in technic each year. The results have been approximately the same, with perhaps some improvement each year until the use of local applications of pollen solution to the nasal mucous membrane was added last year. This increased very materially the number of good results. The following plans, in brief, were employed.

First Method. Whole pollen of small ragweed, large ragweed, and golden rod, equally mixed, ground finely and suspended in Lowdermilk's solution was used for the inoculations. This solution was prepared at frequent intervals due to a belief that pollen solutions had a marked tendency to deteriorate even at ice-box temperature. The maximum dose given was 1 mg. of pollen.

Second Method. The second method was like the first except that the solutions were purified by centrifugation at high speed.

Third Method. Several pollens were each weighed out separately in 10 mg. lots and kept in wax papers in a desiccator. A specimen of each was ground up finely at weekly intervals, suspended in Lowdermilk's solution and given in increasing doses, each patient being given the pollen to which he was sensitive. The use of this method seemed to yield better results than the previous ones.

Fourth Method. Each of some twenty pollens, common to this district, were ground up separately with sand in 500 mg. to 5-gram lots, were suspended in Lowdermilk's or Coca's solution, (1 per cent suspension) and clarified after several days by sedimentation. Toluol was added to this mixture last year (at Coca's suggestion) as a preservative. This preparation seemed to keep potent for several months at ice-box temperature. Its use saved the laborious process of preparing fresh suspensions each week. (NOTE. The plan of making suspensions sufficient in quantity to last an entire season is recommended since by its use the preparation of fresh stock solutions of somewhat greater potency than the old ones is avoided. Coca's method of filtering his preparations through a stone filter seems a valuable addition in technic, although no infections were obtained through our use of stock solutions as above prepared.)

From each stock solution, serial dilutions were made at weekly intervals and kept at ice-box temperature. In the treatment of patients those extracts were chosen for use which produced a positive conjunctival reaction in a 1 to 1000 dilution. When none of the pollens gave positive conjunctival tests, as happened in several instances, those pollens were chosen which gave the strongest intracutaneous tests. The following plan of administration was used:

Treatment was commenced, when possible, in June. In many instances, treatment was started much later than this, and even at the beginning of and during the pollen season. For the initial dose 0.1 cc of a solution containing 0.001 mg. of pollen to the cc was used in every instance. The injections were given each day and the dose doubled each day, that is, patients were given 0.1 cc on the first day, 0.2 on the second, 0.4 cc on the third, 0.8 cc on the fourth, and on the fifth 0.1 cc of solution ten times as strong, that is, a dilution of which 1 cc contained 0.01 mg. of pollen. This increase in dosage and concentration of solution was continued until a dose of 0.25 cc to 0.5 cc of a 1 per cent solution was reached—that is, a solution of which 1 cc contained 10 mg. of pollen. When this, the maximum dose, was reached, the interval was spaced out to from three to six days, and this dose was repeated when possible up until a few days before time for the pollen season to commence. It was then discontinued. When there was need for haste because of the approach of the pollen season the injections were given twice daily instead of once daily. These patients gained tolerance more rapidly and reacted less it seemed than the others. This method, I believe, will become the method of choice.

Patients who failed to show signs of hay-fever after the season was well started were given no further treatment. Those who developed hay-fever, however, or who seemed to be less than 75 per cent relieved, or who had been insufficiently treated subcutaneously because of starting late, were given local treatments in the following way:

Local Treatment with Pollen. At daily intervals a mixture of several 1 per cent suspensions of the more important pollens of this district, namely, the three ragweeds, cocklebur, sages, marsh-elder, and lamb's-quarter, were sprayed into each eye and into each nostril. Following this there was almost invariably a marked attack of hay-fever, which in some instances, required adrenalin locally for relief. After this administration had been given for a few days, the reactions after treatment, almost without exception, became less marked, and after 5 to 10 treatments, disappeared almost completely. At the end of 10 treatments, the patients were almost without exception relieved of hay-fever, or partly relieved. The treatments were discontinued when marked relief was obtained. The mixture of pollens as above mentioned was used in preference to solutions of the individual pollens because of a belief that pollens other than the ones which gave positive tests might have played contributory roles in the causation of symptoms. Patients sensitive to pollen not contained in the mixture were treated with the pollens to which they reacted.

Modifications to Avoid Reactions. While the plan of subcutaneous treatment, as above described, was carried out when things went smoothly, it was by no means adhered to in every case, especially

in patients who had not arrived at a high dosage before the pollen season commenced. In more than 50 per cent of the cases the treatment was modified on account of a tendency to react or on account of our fear of the same, and the dose of pollen was either increased less rapidly, repeated, or even reduced in amount at times. Often, also, the intervals between injections were lengthened. In individuals whose local reaction did not subside almost completely within twenty-four hours, the time interval was as a rule lengthened to forty-eight hours or even to three or four days. The endeavor was made not to give a dose until the effects of the previous one had almost entirely worn off.

The above plan of treatment is not recommended to physicians who are not thoroughly experienced in the use of pollen, since pollen reactions can be very severe, alarming, and even dangerous. Whereas we have never as yet had a mishap nor an alarming reaction in pollen therapy, we attribute this partly to the fact that patients have not been allowed to leave the office for a half to one hour after receiving injections and adrenalin has been administered freely and quickly whenever signs of reaction appeared. It has been due also to the fact that we have avoided increasing the dose of pollen too rapidly and have avoided making the interval between injections too short in patients in whom a tendency to react was noticed. The above plan is safe I believe in the hands of physicians experienced in pollen therapy; in fact, our severest reactions have not been obtained with the higher doses of pollen nor in patients in whom this plan was carried out perfectly, but in patients who, for some reason, did not take treatment regularly and in patients who were being tested intracutaneously. Patients who stop therapy for two weeks or more are likely to react strongly when treatment is resumed unless the dose is reduced.

In addition to the pollen treatment as above outlined, patients who gave positive intracutaneous tests to fruits, vegetables, grains or dander (and this was true of the great majority of patients) were asked to avoid during the pollen season those substances to which they gave positive skin tests. Some of the patients noticed, on testing themselves out, that such substances caused an actual increase in their tendency to have hay-fever. Others noticed no untoward effect. In the latter case, they were allowed to chose any diet they desired.

In addition to this, patients who had a tendency to have hay-fever were advised to wear goggles at times (even at night) when they were exposed to pollens; to avoid pollen so far as possible by keeping in downtown districts, keeping the windows closed, and avoiding trips in the country, railroad trips, etc., and to apply the following lotion to their conjunctiva and nasal mucous membrane when needed: Adrenalin (1 to 1000 solution), 1 cc; resorcin solution (3 per cent), 31 cc.

It is important also for patients with a tendency to pollen asthma to avoid mouth-breathing if possible, for frequently when the nose is stopped up and mouth breathing is practised, pollen asthma will start.

Theoretical Reasons for the Above Methods of Therapy. One's first impression of pollen therapy is that it is analogous to vaccine therapy. One is inclined, therefore, to follow methods learned from the use of vaccine and tuberculin therapy. This is a mistake, for pollen therapy and vaccine therapy are quite different. The reaction from vaccine injections appears slowly—that is, after a period of hours. Also, the immunity gained appears slowly—that is, after a period of hours or days. The reaction in an allergy patient, however, after an injection with pollen appears almost immediately—that is, in a matter of minutes or seconds. Tolerance likewise appears quickly. This is true not only of pollen when given subcutaneously but also when applied locally. For this reason, one should expect a better result from injections when given at shorter intervals.

Local applications of pollen solution were made on the basis of a report by McKenzie, who found that the intracutaneous injection of allergen in a sensitive patient gave rise to increased tolerance in the skin around the inoculated area. The writer had an excellent opportunity of verifying this work through the study of a patient whose skin was highly sensitive to light. It was observed in this patient that the application of winter afternoon sunlight to the skin for a period of two and a half minutes gave rise to a hive which would cover the entire area exposed. This gave rise to local immunity in the exposed area so that further exposure the same day would cause less reaction. The immunity so gained was lost after twenty-four to forty-eight hours. Repeated exposures on consecutive days gave rise to a high grade of local immunity so that eventually a twenty-minute exposure would give rise to less reaction than originally followed a two-and-a-half-minute exposure.

Inasmuch as the reaction and immunity appeared so quickly in the light case and inasmuch as reactions appear so quickly after subcutaneous treatment with pollens, it seems more logical to give the pollen at frequent intervals than it does at longer intervals. One is more likely thus to give his injections during a period of relative tolerance and reactions should be less frequent and less severe. This actually appeared to be the case in my experience for during one entire season this year we did not have one single marked constitutional reaction. In previous years one reaction was obtained on an average for every second case or for every sixtieth dose of pollen. These reactions appeared, as a rule, however, in patients who did not receive pollen treatment regularly

and occasionally, no doubt, was due to the injection of a small amount of extract into a capillary or venule.

The advantages in the above plan in therapy lies chiefly in the rapidity with which patients can be given tolerance for pollen. The giving of pollen at greater intervals with smaller rate of increase in dosage lengthens greatly the time required for treatment. Months are required before any marked grade of tolerance is established. It is difficult to keep patients under observation for prolonged periods and this treatment carried out with the help of physicians inexperienced in pollen therapy is notoriously unsatisfactory. By the use of daily injections the dosage can usually be increased rapidly to the point where concentrated solutions can be used.

Treatment of Reaction. It is a good rule to keep patients in the office for one hour after the injection of pollen extracts. If they complain of itching or redness of the skin, swelling of the tongue, a feeling of oppression in the chest, cough or wheezing, or of symptoms resembling hay-fever or of pain in the back, 0.5 cc of adrenalin (1 to 1000 solution) subcutaneously should be given immediately. If the reaction shows no sign of abating within three or four minutes, this dose should be repeated. If no signs of improvement occur within several minutes it should be repeated a third time or oftener. Atropine $\frac{1}{100}$ grain subcutaneously should also be used. We have never observed a single reaction within a period of seven years, which has not responded readily to treatment administered in this way.

Results of Pollen Therapy. No results are more irregular than those which follow pollen therapy, unless treatment is adequately and carefully administered. When treatment is adequately administered, few fail to get partial or complete relief if the correct pollens are used. If treatment is inadequately administered, the percentage of cases relieved, hardly reaches 50 per cent.

Of the cases treated in our clinic last season, 62 in number, only 10 per cent failed to get marked relief. None of this 10 per cent were given local treatments in the nose. They had received adequate subcutaneous treatment, however. Of the cases which had received subcutaneous treatment 39 per cent returned after the beginning of the pollen season with symptoms of hay-fever, although as a rule not so severe as usual. The remainder were either free of symptoms, or so nearly free that no further treatment was given. Of the 39 per cent who were not relieved, practically all who received intranasal treatment were relieved partially or completely. Four cases who were relieved at the beginning of the season developed symptoms, although milder than usual in grade, toward the end of the season.

It has appeared to us on the whole, that patients with pollen hay-fever and asthma are as a rule either relatively easy to relieve,

or rather difficult to relieve. Of the former group, pollen therapy according to almost any plan seems to give partial or complete relief. Relief seems to persist, in many cases, for several seasons. Of the latter group, that is, the group who are difficult to relieve, the use of intranasal treatments increased the ratio of success more than any other modification of the method which we have ever used.

It is impossible to surmise in advance, which patients will be relieved most easily and to what extent treatment will have to be pushed. For example, one patient who had been subject to pollen hay-fever for forty-five years and who had never been able to obtain relief, except by a very wide change in geographical situation, gave one of the best therapeutic results from subcutaneous treatment alone. She was given 25 doses of pollen extract subcutaneously with maximum dose of 0.5 cc of a 1 per cent suspension of pollen and reacted mildly several times so that the routine had to be modified. In spite of this, she was so relieved of her sensitiveness, that she did not require local applications of pollen, and was able to disregard any of the weeds in her locality during the entire pollen season.

Another patient, who had been subject to severe hay-fever for a number of years, came for treatment several days after the pollen season had commenced. He gave a marked constitutional reaction which required adrenalin when the intracutaneous tests were applied. He was given shortly afterward an intranasal and ophthalmic treatment with pollen extract. He could not take further treatment of any sort. His hay-fever disappeared completely, however, after the reaction to pollen extract subsided and he went through the remainder of the season symptom-free.

Another patient, who had been subject to hay-fever and asthma of great severity for many years, was given 16 injections of pollen extract with a maximum dose of 1 mg. of pollen in 1916. He was given a series of 21 doses the following year with a maximum dose of 1 mg. He has remained clinically free of both hay-fever and asthma since the treatment was originally started.

Summary of Pollen Therapy. Whereas, marked irregularities in result are interesting and rather frequent, it can be said in summarizing, that the more consistently pollen treatment is given, the better the result is likely to be, and that if a patient is treated thoroughly with pollen subcutaneously and intranasally, a bad result should make one suspect an error in diagnosis.

Specific Therapy with Proteins other than Pollen. My experience in the specific treatment of hypersensitiveness with proteins other than pollen is rather small and has been confined to therapy with milk and egg. It has been possible in the majority of our cases for the patient to avoid substances responsible for illnesses, so that specific therapy was not necessary. This type of therapy

has not been so successful on the whole as therapy with pollen extract. This is believed to be the case for a very good reason. Patients who react to pollen are sensitive to the substance as encountered by the patient, while patients sensitive to a food may be sensitive to a digestive product. In the latter case, subcutaneous treatment with the protein as prepared in a laboratory would seem theoretically illogical. Treatment by mouth should offer more hope of success. In one patient sensitive to milk, tolerance was so increased by subcutaneous treatment and treatment by mouth that he was eventually able to take almost unlimited quantities of milk without his original symptoms, hives and asthma. A new symptom, however, namely diarrhea, began to follow the ingestion of milk.

In a patient sensitive to ovomucoid a few drops of a very dilute solution of egg by mouth or hypodermically caused asthma. Tolerance for egg subcutaneously was increased to a point where he could stand a relatively large dose without ill effect. It was never possible, however, to increase his tolerance for egg by mouth to a point where he could take more than 8 drops of a solution prepared by mixing 1 drop of whole egg with 250 cc of salt solution. Treatment by mouth was carried out faithfully by the mother over a period of six months but ended in failure.

Non-specific Protein Treatment. In spite of one's like or dislike for the use of arbitrary remedies in the practice of medicine, it is in the present state of our knowledge advisable to use them at times. This may be said of non-specific protein therapy in the treatment of allergy. Non-specific protein therapy can occasionally be used with a fair or even brilliant therapeutic result in the treatment of chronic asthma, chronic gastro-intestinal disturbances, eczema, and other disorders (occurring as part of a general reaction) when no other rational line of therapy presents itself. It is not recommended in the treatment of local reactions due to contact. It is excusable today to try it in general cases when the primary source of this disorder cannot be found or removed, or if no other more logical method of therapy presents itself.

It is not necessary to discuss non-specific protein therapy broadly in this connection. Suffice it to say that it has an influence upon immunity and, under certain circumstances, has an influence upon the functional activity of organs supplied by the vegetative nervous system. The following case is cited to illustrate how marked this influence may be.

The patient, a woman, aged thirty-five years, had been for many months, a victim of dyspepsia. The appendix and the gall-bladder had been removed. The stomach and duodenal bulb had been found anatomically normal at operation. At the time she came to me she was complaining of pain in the epigastrium, worse after eating, and associated frequently with nausea and vomiting. The

pain was brought on by almost any type of food, especially if taken in more than very small amounts. She had at the same time, colon bacillus pyelitis and cystitis. The stomach upon fluoroscopical examination showed a high grade of spasticity and hyperperistalsis; in fact, in this respect, it exceeded any which I have examined. The picture was that of four or five large balls of barium which extended across the abdomen. During the treatment for pyelitis, she was given a small dose of autogenous colon bacillus vaccine subcutaneously. She had a profound reaction after this with chill, high fever and general malaise. She returned the following day to say that her stomach had been cured by the vaccine. It was examined again and was found to have changed from its previous condition of spasticity into a relaxed bag, which almost filled the abdomen. Peristaltic waves were hardly visible. Food no longer caused discomfort or nausea and the patient suffered no marked gastric disorder for months.

Without discussing the mechanism through which non-specific protein therapy may exert its influence, suffice it to say that under certain conditions it has the practical effect of modifying the activity of certain organs supplied by the vagus and sympathetic nerves. Upon this basis I have used it occasionally as a remedy in the treatment of asthma, gastro-intestinal neurosis, dermatosis, and other general manifestations of allergy. The following case is cited as an example of the effect it can have in asthma.

The patient, a woman, aged fifty years, was brought into my office by the police with the statement that she had fallen unconscious on the street and was thought to be in a dying condition. She proved to have a very severe case of asthma of unknown origin and of long standing. She was given palliative remedies with a little temporary relief. She was later given 10,000,000 colon bacilli intravenously. A reaction followed with chill, high fever, malaise, and other symptoms. At the height of the reaction the bronchial tubes relaxed and she was able to breath freely for the first time in weeks. She remained nearly free of symptoms for about two months when her asthma recurred.

We have chosen colon bacilli for use in non-specific protein therapy because patients are almost always sensitive to colon bacillus protein and it seems to be the reaction which does good. Colon bacillus injected intracutaneously almost always gives rise to a marked local inflammatory reaction within twenty-four hours. If injected subcutaneously or intravenously in small doses, it almost always gives a marked constitutional reaction. As a rule, the subcutaneous treatment is preferable. If this fails a smaller dose, roughly one-fifth to one-tenth the subcutaneous dose, can be used intravenously.

The effect of this treatment, while occasionally very beneficial, is rarely permanent. Relief, if obtained, may last for two to six months but rarely longer.

SUMMARY OF NON-SPECIFIC PROTEIN THERAPY. Through the use of colon bacilli subcutaneously or intravenously in very small doses, non-specific protein therapy can be recommended in the treatment of general allergy if the more logical methods cannot be used for any reason or fail. Good results, if obtained, are rarely permanent. It apparently does little or no good in contact allergy and is not recommended for this.

Symptomatic Treatment. It does not come within the scope of this paper to discuss at length the symptomatic treatment of asthma and allied conditions for few subjects have been more thoroughly discussed in medical literature than this.

Adrenalin. Adrenalin is the one remedy which is relatively consistent in its effect. Other remedies, even atropine, are characterized by their inconsistency. A remedy which completely relieves one patient may have no marked influence on others. Adrenalin is also our most effective symptomatic remedy, and if properly used, will relieve the great majority of cases temporarily. The dose required varies, in fact, varies from 0.05 or 0.1 to 1 or 2 cc. In order to obtain the best effect, the dose must be adjusted to suit the individual's need. This can be accomplished usually by giving 0.25 to 0.5 cc of a 1 to 1000 solution subcutaneously at five- or ten-minute intervals until the patient experiences relief of symptoms or symptoms of reaction to adrenalin, such as nervousness, pallor, and tremor of the hands. When the amount required for relief has been determined in this way, the total amount used can be repeated, if given slowly, so often as symptoms return. In this way, continuous relief can often be obtained. After the patient has been free of symptoms for a time, the dose can often be reduced—in fact, can often be reduced gradually from a relatively large dose to a dose of 0.1 or 0.2 cc. Occasionally, however, this is not the case and larger doses have to be used and continued in order to maintain relief. Adrenalin should be repeated as soon as possible after symptoms begin to return; in fact, it is well to anticipate the return of symptoms by a few minutes if this can be done.

Adrenalin gives relief in the majority of cases of asthma. It often fails in angioneurotic edema where very large doses are frequently required. It does not give immediate relief in eczema and other illnesses where structural changes in the tissues have occurred.

Adrenalin can be used for weeks or months without serious ill effect although, perhaps, more experience is needed before the harmlessness of this drug can be relied upon if used for indefinite periods of time. I have observed several cases in which it has been used for months with apparently no serious ill effect. While adrenalin can be used continuously for months, it is best adapted for emergency treatment and temporary treatment and should

be discontinued as soon as measures which have a more lasting effect can be instituted.

Pituitrin. Pituitrin given subcutaneously often has an effect somewhat similar to that of adrenalin. Its immediate effect is not nearly so marked but as a rule, if the drug is effective, it gives a longer period of relief than adrenalin. It is occasionally advisable to use pituitrin and adrenalin together. Koessler warns against the use of pituitrin on account of its usually containing histamine as an impurity.

Atropine. Atropine in doses of $\frac{1}{300}$ to $\frac{1}{100}$ grain given two or three times in twenty-four hours subcutaneously or by mouth, is often valuable. It can be used in conjunction with adrenalin or it can be used alone. A dose should be used which causes dryness of the mouth but rarely a dose which causes blurred vision or dilation of the pupils. Often atropine in small doses marks the difference between success and failure in the relief of patients who have been treated according to the principals outlined earlier in the paper. A patient nearly relieved by other means often may be completely relieved with the help of atropine.

Habit Forming Drugs. Habit forming drugs need no detailed discussion in this paper since they are contraindicated in most chronic illnesses, especially in asthma. Emergencies which justify their use rarely occur.

To Summarize Symptomatic Treatment. To summarize symptomatic treatment, adrenalin, pituitrin, and atropine should be looked upon as useful symptomatic remedies, best adapted, however, for temporary use while the more lasting methods of treatment are being instituted.

General Summary and Conclusions. The numerous manifestations of allergy, such as hay-fever, asthma, the dermatoses, the gastro-intestinal, urological, and neurological symptoms, urticaria, angio-neurotic edema hypotension, etc., can be treated along five different lines, namely, avoidance or removal of the specific cause of illness, avoidance or removal of contributory causes, specific protein treatment, non-specific protein treatment, and symptomatic treatment.

Avoidance or removal of the specific cause is the method of choice when this method can be used.

Specific protein treatment is the method of choice when the specific cause of illness is known, but cannot be conveniently avoided, namely, in the case of sensitiveness to the common fall pollens and to cooked egg, milk, or wheat.

When the specific cause of illness is not known or cannot be removed or treated specifically non-specific protein treatment is worthy of trial. This can be accomplished best, I believe, through the use of colon bacilli subcutaneously or in very small doses intravenously.

Adrenalin, pituitrin, and atropine are useful symptomatic remedies well adapted for emergency use and for temporary use while the more lasting methods of treatment are being instituted.

The results of pollen therapy in the treatment of pollen hay-fever and asthma are good. The best results are obtained through the use of pollen extract subcutaneously, combined with local applications of pollen extract to the conjunctivæ and nasal mucous membrane.

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NON-SPECIFIC VERSUS SPECIFIC THERAPY IN BRONCHIAL ASTHMA.

By NATHAN S. SCHIFF, M.D.,
ASSOCIATE IN MEDICINE, NEW YORK.

(From the Medical Department of the New York Post-Graduate Medical School and Hospital.)

THE modern conception of anaphylaxis, as the cause of asthma, is based upon the experiments of Auer and Lewis,[1] who showed that bronchospasm was one of the characteristic results of anaphylactic shock in the guinea-pig. Meltzer,[2] impressed with the similarity of these bronchospasms to asthmatic seizures suggested that asthma was an anaphylactic phenomenon. Since then the epochal work of Walker,[3] and the work of Schloss,[4] Cooke,[5] Longcope,[6] and Rackemann,[7] have shown that in 40 to 50 per cent of asthmatic cases the condition is due to sensitization to food, epidermal, bacterial or pollen protein.

The specific protein therapy, following the determination by various methods of sensitiveness to proteins, is excellently carried on by Walker,[3] Cooke,[5] Schloss,[4] Rackemann[7] and others. Autogenous vaccines from the sputum and foci of infection have also been utilized with success. Non-specific protein therapy, however, has been barely touched upon, although there is every reason to believe that even in the so-called specific protein therapy, a non-specific element plays an important part. The analogy to other fields shows this to some degree. Meyer[8] has pointed out that besides the specific antitoxin value of serum, in diphtheria, the horse serum protein contains a non-specific stimulating element. In the process of concentration this non-specific factor is naturally lost to a considerable degree, this fact justifying the repeatedly expressed criticism of late years, that the modern highly concentrated serum seems less effective than the old serum which was lower in antitoxic units. R. F. Vaccarezza[9] and his associates recently reported that in 100 cases of anthrax they found normal beef serum as effective as specific antiserum. They attributed this action to the protein element in the serum. Requiring a substance which does not sensitize, they substituted peptone and adapted it to their purpose. The results proved so satisfactory that they now use it exclusively even in septicemia.

Literature on non-specific therapy in bronchial asthma is meager. Auld[10] reported the use of peptone subcutaneously and intravenously. Pagniez and Widal[11] and Abrami and Brissaud[12] utilized peptone by mouth. Boyd[13] claimed success with intravenous injections of typhoid vaccine (50,000,000).

Impressed with the effects of autogenous vaccines in my treat-

ment of non-sensitive patients, I became doubtful as to whether I was dealing with a specific bacterial antigen, or whether the results obtained were merely the benefits of a non-specific action. This uncertainty was further strengthened by observing that recurrences after vaccine therapy could be relieved by other vaccines containing totally different organisms.

To determine the question, a preliminary test for sensitiveness to proteins was made on all patients admitted to the hospital. Approximately ninety tests were made on each patient by the cutaneous method. Cardiorenal factors and other reflex phenomena were excluded in the routine examination. Sensitive patients were divided into five groups, according to whether they had received: (1) Specific desensitization, (2) autogenous vaccines, (3) milk, (4) peptone, or (5) no treatment whatever, these last having been relieved from asthma after the offending protein was removed. The unclassified or non-sensitive patients were divided into three groups, depending on whether they had received: (1) Peptone, (2) milk or (3) autogenous vaccine.

PREPARATION OF MATERIALS. *Peptone.* A 33.33 per cent solution was prepared by mixing peptone, glycerin and water. The mixture of water and glycerin was added to Armour's peptone siccum (dry) slowly, rubbed well by means of a mortar and pestle, warmed gently over a water-bath with constant stirring until solution was complete, and then filtered until clear. This solution stands sterilization and will keep under any condition, no ice being necessary. The filtered preparation was then poured into a small, glass, rubber-capped vial and sterilized in an autoclave or water-bath for from thirty to forty minutes.

Milk. Straight whole milk was poured into a 2-ounce, rubber-capped bottle and placed in a water-bath up to the neck of the bottle and allowed to boil for one hour.

Vaccines. Sterile containers were furnished to patients with instructions to bring a specimen of the sputum expectorated after a severe coughing attack that is, from the deeper bronchi.

Blood-agar plates were streaked, and a loopful of the sputum was inoculated in 50 cc of 1 per cent dextrose broth, which was from 0.2 to 0.5 per cent acid. These cultures were then incubated for twenty-four hours. The blood plates were studied for the type of organism present, and a Gram stain was made of the broth culture to rule out contaminating organisms. The broth culture was then centrifuged at high speed (1500 revolutions per minute) for fifteen minutes and the supernatant broth discarded. The precipitate was washed in sterile normal salt solution and centrifuged at high speed, the bacteria being thrown down. The filtrate was suspended in 5 cc of fresh normal salt solution, put in an ampoule, and placed in a water-bath at 60° C. for one hour. This suspension was tested for sterility in dextrose broth, and then

diluted with normal salt solution so that 1 cc was equivalent to 1,000,000,000 organisms, as shown on the blood plates.

METHOD OF ADMINISTRATION AND DOSAGE. *Specific Therapy.* Patients sensitive to epidermal proteins were treated with commercial preparations* supplied in dilutions of 1:100,000, 1:10,000, 1:1000 and 1:500. To determine the initial therapeutic dose, Walker's[14] method of testing for the degree of sensitiveness was carried out. Treatment began with 0.2 cc of the weakest solution failing to give a reaction by the dilution test. This was usually a 1:10,000 or a 1:100,000 solution. This dose was increased by 0.1 cc every five days, so that three doses of each dilution were administered, ending with six minims of a 1:500 solution.

Autogenous Vaccines. All vaccines were prepared so that 1 cc was equivalent to 1,000,000,000 organisms. The initial dose was 200,000,000 bacteria (3 minims), except that to sensitive patients one-half this dose was given. The dose was increased by 1 minim at triweekly intervals until 1 cc was given. This last dose was occasionally repeated two or three times at biweekly intervals.

Peptone. Three minims of the solution described proved a safe initial dose. This was increased by 1 minim at biweekly or triweekly intervals up to 1 cc.

Milk. Five-tenths to 1 cc was the initial dose administered. This was increased by 0.5 to 1 cc at triweekly intervals up to 3 cc, which dose was never exceeded. In some cases the 2-cc dose was never exceeded.

Comment. Experience alone can enable one to decide the dosage, which must be determined according to the symptoms and progress in the case. In the event of a severe local reaction with any of the above preparations, the preceding dose should be repeated. Early recognition of the approach to the limit of tolerance is important. The first symptoms are nausea with vaccine; drowsiness and chilliness with peptone; epistaxis and bilateral frontal headaches with milk. (Epistaxis, in which a few drops of blood were lost three or four times a day, for one or two days, occurred in 3 cases.) If any of these symptoms arise during the treatment, it is advisable to repeat the last dose and thereafter increase cautiously approximately one-half the usual increase.

TABLE I.—EFFECT OF PROTEIN THERAPY ON SENSITIVE PATIENTS.

Treatment.	No. of patients.	Relieved of asthma.	Markedly improved.	Unimproved.
Milk	10	4 (40.0 per cent)	5 (50.0 per cent)	1 (10.0 per cent)
Peptone	3	2 (66.6 ")	0	1 (33.3 ")
Vaccine (autogenous)	14	5 (35.7 ")	6 (42.9 ")	3 (21.4 ")
Specific therapy . .	11	5 (45.4 ")	3 (27.3 ")	3 (27.3 ")
Omission	7	7 (100.0 ")	0	0

* Arlington Chemical Company's products used exclusively.

Of the 10 sensitive patients on milk therapy none gave a hereditary history. Three were positive to epidermal and food proteins; 4 to epidermal; 1 to food and pollen; 1 to food; 1 to pollen. Two were changed from vaccine and relieved of asthma; 1 was changed from peptone and markedly improved; 1 was changed to vaccine with no improvement. Eight were males, and 2 were females; ages eighteen to fifty-six years. The duration of the disease was two to forty-nine years. One was changed from specific therapy and markedly improved.

Of the 3 sensitive patients on peptone therapy, none gave a hereditary history. All patients were positive to an epidermal protein. One was changed from vaccine and relieved of asthma; 1 was changed to milk and markedly improved. Two were males, and 1 was a female; ages forty to fifty-four years. The duration of the disease was eight to fourteen years.

Of the 14 sensitive patients on autogenous vaccine therapy, 3 gave a hereditary history. Six were positive to an epidermal protein; 2 to food; 2 to pollen; 2 to bacteria; 1 to epidermal protein and food; 1 to pollen and food. Two were changed to milk and relieved of asthma; 1 was changed from milk and unimproved; 1 was changed to peptone and relieved of asthma. Nine were males and 6 were females; ages, fourteen to forty-nine years. The duration of the disease was one to thirty years.

Of the 7 sensitive patients to whom no treatment was given, 2 gave a hereditary history. Six were positive to epidermal proteins and 1 to food. Four were males and 3 were females; ages, twenty-one to forty-eight years. The duration of the disease was one month to twenty-nine years.

TABLE II.—EFFECT OF PROTEIN THERAPY ON NON-SENSITIVE OR UNCLASSIFIED PATIENTS.

Treatment.	No. of patients.	Relieved of asthma.	Markedly improved.	Unimproved.
Milk	8	6 (75.0 per cent)	1 (12.5 per cent)	1 (12.5 per cent)
Peptone	8	5 (62.5 ")	3 (37.5 ")	0
Vaccine (autogenous)	43	20 (46.4 ")	20 (46.4 ")	3 (7.2 ")

Of the 8 non-sensitive patients on milk therapy, 3 gave a hereditary history. Four were males and 4 were females; ages, twenty-five to fifty-nine years. The duration of the disease was four months to thirty-nine years.

Of the 8 non-sensitive patients on peptone therapy, 1 gave a hereditary history. Four were males and 4 were females; ages, fourteen to fifty-one years. The duration of disease was five weeks to twelve years. One was changed from vaccine and relieved of asthma.

Of the 43 patients on autogenous vaccine therapy, 15 gave a hereditary history. Twenty were males and 23 were females; ages, ten to seventy years. The duration of the disease was four months to forty-four years. One was changed to peptone and relieved of asthma.

Report of Cases.—CASE I.—E. U., a man, aged thirty-eight years, entered the hospital, August 24, 1922, complaining of having had for two years continual attacks of asthma with paroxysmal coughing and dyspnea between 2 A.M. and 5 A.M. and attacks of coughing during the day. He had pneumonia and empyema with thoracotomy when nine years of age, and had frequent attacks of bronchitis thereafter. Physical examination of the chest revealed emphysema and bronchitis, and a thickened pleura on the right side beneath the ninth rib (below the scar of his previous operation). The roentgenological examination verified this finding, and showed a considerable elevation of the right diaphragm (pleurodiaphragmatic adhesions) and a generalized thickening of the bronchial wall, with accentuation of the pulmonic markings, especially the right lower lobe. Cultures of the sputum were made and a hemolytic streptococcus as well as a staphylococcus was recovered. The urine and Wassermann tests were negative. The cutaneous tests showed a positive reaction with the pollen (corn).

On September 19 he received 1 cc of milk, injected subcutaneously. On September 21 and thereafter at weekly intervals 2 cc were injected. On October 26 and 31, 3 cc were injected.

Comment. Following the second injection, the paroxysmal dyspnea ceased and the patient had but one paroxysmal attack, on October 26. Since his discharge on October 31 an occasional cough has been the only symptom. Examination of the chest, January 17, 1923, showed emphysema, thickened pleura, right base and only an occasional rale.

CASE II.—M. W., a woman, aged twenty-five years, entered the hospital, December 22, 1922, complaining of having had asthma for the preceding two or three years, the attacks lasting from seven to ten days, the longest free interval being two weeks. After violent coughing she expelled some sputum mucopurulent in character.

Physical examination of the chest revealed emphysema with marked bronchitis. Cultures of the sputum were made and a Staphylococcus aureus was recovered. The urine and chemical blood examinations were normal, and the Wassermann negative. The cutaneous tests showed a 1+ reaction to cat hair and lobster.

She received six injections of milk, subcutaneously, beginning with 0.5 cc up to 3 cc, at biweekly intervals, ending January

30, 1923. Following the second injection she was relieved of asthma.

Comment. This patient had not changed her daily routine, for she was not informed of her sensitiveness to cat hair and lobster until February 6, 1923, when she reported that she was still free from all symptoms.

CASE III.—F. H., a man, aged fifty-two years, entered the hospital, November 9, 1922, complaining of having had asthma for forty-nine years, the attacks being continual all the year round, lasting two hours or more, with coughing, wheezing and expectoration between paroxysms. He had some expectoration of thin gray sputum.

Physical examination of the chest revealed emphysema and typical music-box findings. The patient also had chronic myocarditis and a right inguinal hernia. He had received treatment at one of the New York asthma clinics for one year without results. Cultures of the sputum were made and a pneumococcus, a hemolytic streptococcus and a green streptococcus were recovered, from which a vaccine was prepared. The Wassermann and urine examinations were negative and the cutaneous tests revealed a 2+ reaction to wool.

On January 11, 1923, he received 7 minims of adrenalin chloride (1:1000) for the relief of an acute attack. On January 16, 3 minims of his autogenous vaccine were injected. On January 18 and 20, 4 and 5 minims, respectively, were injected, followed by an aggravation of his symptoms. On January 23 his treatment was changed to milk injections. He has now received six injections at biweekly intervals and is markedly improved. He still has short attacks, mild in character, lasting half an hour, but his sleep is now practically undisturbed. He showed a good local reaction after each injection, but no constitutional symptoms.

CASE IV.—A. R., a man, aged fifty-six years, entered the hospital, December 30, 1922, complaining of having had asthma for eleven years, the attacks lasting from five to seven days, the longest free interval being one week. Coughing between attacks was constant. The burning of asthma powder gave relief.

Physical examination of the chest revealed emphysema with bronchitis. He also had a high-grade pyorrhea, an enteroptosis, and a right inguinal hernia. The heart sounds were of poor muscular quality.

The cutaneous tests showed a 1+ reaction to tomatoes and coffee.

He received six injections of milk, beginning with 1 cc and gradually increasing to 3 cc, at biweekly intervals; with an absence of paroxysms since the initial injection, January 23, 1923. On February 15 he reported himself free from attacks.

CASE V.—A. B., a man, aged forty years, entered the hospital, September, 1921, complaining of having had asthma for ten years, the attacks being continual but severest during the winter months, lasting about a month, with the longest free interval of two weeks. He gave a history of syphilis of four years' duration.

Physical examination of the chest revealed emphysema with bronchitis. The Wassermann showed a 3+ reaction. The cutaneous tests showed a 2+ reaction to rabbit hair.

Desensitization was instituted and he was discharged in December, 1921, relieved of asthma. He returned December 14, 1922, complaining of having had attacks of asthma for the preceding three weeks. These attacks were so severe that he was confined to his home for that period. On physical examination the findings were identical with those on the first admission. The cutaneous tests showed a 2+ reaction to goose feathers and a negative reaction with rabbit hair. He received nine injections of milk, beginning with 1 cc, December 21, 1922, and gradually increasing up to 2.5 cc at biweekly and triweekly intervals. Following his second injection he was free from asthma. On February 8 he reported that he was entirely free from symptoms.

Comment. This patient, originally sensitive to rabbit hair, was entirely free for about one year following specific desensitization. On readmission the cutaneous tests showed that he was then sensitive to a different epidermal protein—goose feathers. He is now entirely free from symptoms following non-specific therapy —milk. Syphilis apparently played no part in this picture for he had received no antisyphilitic treatment at any time.

CASE VI.—A. D., a man, aged fifty-four years, entered the hospital, September 27, 1922, complaining of having had asthma since 1911, the attacks occurring all the year 'round and being worse during the summer months.

Physical examination of the chest revealed emphysema with typical music-box findings. He also had a marked pyorrhea and a high-grade enteroptosis. The red blood count was 4,328,000; white blood count, 17,800; polymorphonuclear cells, 17 per cent; lymphocytes, 13 per cent; eosinophils, 4 per cent; transitionals, 5 per cent; mononuclear, 8 per cent; small lymphocytes, 9 per cent; large lymphocytes, 4 per cent; red cells, negative. The cutaneous tests revealed a 1+ reaction to chicken feathers and a ± reaction to ragweed short and ragweed giant.

On November 2, 1922, he received 3 minims of peptone subcutaneously. This dose was increased by 1 minim at weekly intervals for six doses with no improvement. There was no local reaction following any of the injections. On December 19, 1 cc of milk was injected subcutaneously and thereafter at weekly intervals 2.5 cc were injected for five doses. He had one attack

on January 13, lasting two hours, following the fourth dose. A good local reaction followed each injection.

Comments. This patient, sensitive to an epidermal protein and possibly to a pollen protein, did not respond favorably to peptone. Following the first injection of milk, the paroxysms ceased and he has had but one mild attack since. On February 8, a slight cough was the only remaining symptom.

CASE VII.—R. S., a woman, aged fifty-nine years, entered the hospital, November 22, 1922, complaining of having had asthma since April, 1922, the attacks having come on every night with no free intervals, beginning usually at 3 A.M. and associated with dyspnea, paroxysmal coughing and inability to lie in the prone position. The attacks were becoming progressively more severe. She complained of frequent colds prior to the onset of asthma. The chemical blood examination on November 6 showed: Sugar, 0.08 mg.; urea nitrogen, 16.9 mg.; chlorides, as NaCl, 0.5 mg. per 100 cc. The urine and Wassermann examinations were negative.

Physical examination of the chest revealed emphysema with sibilant and sonorous rales throughout. There was a marked enteroptosis and stigmas of ovarian insufficiency. The heart showed an accentuation of the aortic sound; the blood-pressure was 220/120; the cutaneous tests were negative.

Four doses of milk were injected subcutaneously, beginning with 1 cc on January 16; on the 18th, 1.5 cc; on the 23d, 2 cc; on the 30th, 2.5 cc. Following the second dose only a slight cough remained, which did not disturb sleep. On February 13 she was still free from attacks. The blood-pressure on February 6 was 240/120. The chemical blood on February 12 showed: Sugar, 0.14 mg.; urea nitrogen, 13.4 mg.; chloride, as NaCl, 0.5 mg. per 100 cc.

Comment. This case is of interest because of the rather late onset of symptoms, and it also shows that hypertension, in itself, has no bearing on the paroxysms in such a case. The hypertension undoubtedly is part of the menopausal syndrome.

CASE VIII.—R. S., a boy, aged fourteen years, entered the hospital, July 25, 1922, complaining of having had asthma for the past eight years, the attacks being continual, lasting from one to three days, the longest free interval being one week. The urine and cutaneous tests were negative.

Physical examination of the chest revealed emphysema and bronchitis.

Three minims of peptone were injected subcutaneously on August 12. This dose was increased by 1 minim every three, five or seven days; the last seven at weekly intervals, reaching 1 cc on December 16. The 1-cc dose was repeated on December 23,

followed by a one-hour attack, which was the first in five weeks. He reported short attacks on December 27, 28 and 29. Seven minims were injected on December 30, this dose being increased by 1 minim at weekly intervals, reaching 10 minims, January 27, 1923. He has been entirely free from symptoms since December 29, 1922. On February 13 he reported freedom from symptoms, with a gain of 2 pounds over the preceding week.

Comment. During the months that this boy was under treatment he had four short attacks, caused probably by the large doses of peptone administered, which indicates that excessively large doses are not tolerated.

CASE IX.—M. P., a woman, aged forty-one years, entered the hospital, November 9, 1922, complaining of having had asthma since September, 1921, the attacks occurring only during the winter months, lasting one to two weeks, with the longest free interval of two weeks. Between the paroxysmal attacks she had wheezing, coughing and a feeling of tightness in the chest. The urine and Wassermann examinations were negative, and the cutaneous tests showed a ± reaction to duck feathers.

Physical examination of the chest revealed emphysema, with a moderate number of whistling rales at the bases with muffled breath sounds.

On December 12, 1922, 3 minims of peptone were injected. On December 16 she reported having had two severe attacks. Four minims were injected. On December 19 she reported freedom from attacks. She then received 6 minims on December 21, 7 on December 26 and 8 on December 30. January 9 she reported having had a twenty-minute attack following her entrance into a freshly painted room. Eight minims were injected on January 9, with an increase of 1 minim every three days thereafter, reaching 13 minims, January 24, 1923. During this entire time she was without any attack except as noted above. Her last report on February 13 showed that she was still free from attacks.

CASE X.—E. L., a man, aged forty years, entered the hospital, November 17, 1921, complaining of having had asthma for the past fourteen years, the attacks lasting from one to four weeks, the worst period being August to September or continuing on through the winter until May. He also had sneezing, itching of the eyes and lacrimation during the summer months. The sputum was tenacious, the predominating organism being a diplococcus. A few pus cells were present. The cutaneous tests showed a 2+ reaction to dog hair, chicken feathers and sheep wool.

Physical examinations of the chest revealed emphysema and typical music-box findings.

On July 13, 3 minims of peptone were injected subcutaneously.

This dose was increased by 1 minim at biweekly and triweekly intervals until 1 cc was given on August 3. He suffered no attacks following his first injection on July 13. On February 6, 1923 he reported himself still free from attacks.

CASE XI.—R. L., a woman, aged fifty years, entered the hospital, May 23, 1922, complaining of having had asthma for the last eight years, following an attack of bronchitis, the attacks occurring at weekly intervals and lasting about a week. The urine examination was negative. Cultures of the sputum revealed the presence of a hemolytic streptococcus and a pneumococcus, from which a vaccine was made. The cutaneous tests showed a positive reaction to goose feathers.

Physical examination of the chest revealed emphysema. On auscultation the chest was a veritable music box.

June 27, 1922, 3 minims of the vaccine were injected subcutaneously. This dose was increased by 1 minim at biweekly and triweekly intervals to 1 cc, which was reached on July 29, this dose being held for four additional injections to August 17, at which time she reported that she had had no attacks for a period of three weeks. She returned on October 7, with a recurrence, having had attacks for the preceding ten days. Three minims of peptone were injected subcutaneously on that day; on October 10, 4 minims; on October 17, 5 minims; on October 22, 6 minims; she reported no attacks since October 10. She returned on December 7 entirely free from attacks, but had contracted a cold and had a severe cough. A simple expectorant and salicylates were prescribed with benefit. On February 8, she again reported having contracted a cold associated with cough. The same medication was prescribed with relief.

CASE XII.—F. M., a man, aged thirty-nine years, entered the hospital, March 15, 1921, complaining of having had asthma for twenty-nine years, the attacks usually beginning with stomach symptoms, belching of gas or burning sensation in the abdomen, followed by a sense of oppression in the chest, dyspnea and cyanosis, with a feeling of impending death. He had some expectoration of a gelatin-like phlegm. He was always worse on Sunday and believed that tub-bathing aggravated his condition. The attacks would occur continually and would last five days a week. There was a definite hereditary history of asthma. The Wassermann and urine examinations were negative. The sputum was a grayish fluid, with a staphylococcus predominating. The red blood count was 4,272,000; the white blood count, 10,400; the hemoglobin was 80 to 90 per cent (Talquist); polymorphonuclears, 58 per cent; neutrophils, 51 per cent; eosinophils, 6 per cent; basophils, 1 per cent; transitionals, 4 per cent; large mononuclears, 2

per cent; lymphocytes, 35 per cent (18 large and 17 small). The cutaneous tests showed a 4+ reaction to rabbit hair and a ± reaction to dog hair.

Physical examination of the chest revealed emphysema with bronchitis. An enteroptosis and a hydrocele of the left cord about 2 inches in diameter were also present. Further questioning disclosed the fact that the patient had had rabbits in his home for the preceding nine years. Following the removal of the rabbits, with the scrubbing up of the bathroom where these rabbits were housed, and the boiling of all linen there immediately followed complete freedom from attacks. February 7, 1923, he reported himself still free from attacks and that he had not lost a day of work, due to illness, since his discharge, March 17, 1921.

Comment. This man, brought up on a farm, was undoubtedly sensitized to an epidermal protein at the age of ten years, probably that of dog hair. On coming to the city he brought some pet rabbits with him, replacing them from time to time with new ones, thus keeping up his sensitized state. The fact that he was worse on Sunday and that his symptoms were aggravated by tub-bathing was due to the more intimate contact with the offending protein. Regardless of the presence of the various foci of infection he has been entirely free from symptoms since the removal of the rabbits.

Case XIII.—C. T., a woman, aged twenty-nine years, entered the hospital, April 12, 1921, complaining of having had asthma since September, 1920, the attacks occurring about midnight of every third night and lasting until noon of the following day. She had left for Ohio in October and had no attacks during her stay. She returned to her home on December 8 and the attacks returned on December 21, then recurring every third night as before. There was a history of asthma in the family.

Physical examination of the chest revealed emphysema with bronchitis. A seven months' pregnancy was also present.

The cutaneous tests showed a ± reaction with horse dander. By persistent questioning, suspicion was directed toward a rag rug, presented to her as a wedding gift, three weeks prior to her onset of asthma. She was instructed to remove this rug from her home. Returning in two weeks, she reported no attacks in that interval. She was then requested to replace the rug in her home with the result that her attacks returned with the same periodicity. A specimen of this rug was examined, revealing the presence of horse hair. With the permanent removal of the rug she was entirely free from asthmatic seizures until March, 1922. An attack of moderate severity immediately followed a known exposure to horses. Specific desensitization was then instituted, and was completed on June 22.

Comment. The importance of an erythema alone is clearly shown as well as the necessity of diligent search for the possible location of the protein involved. The definite periodicity of the attacks suggests that epidermal proteins have an accumulative action.

Comparative Results with Specific and Non-specific Therapy in Cases of Sensitiveness. A critical analysis of Table I with special reference to the results obtained by the various methods used is my strongest evidence at present in favor of non-specific therapy in the treatment of asthma more or less as a routine measure, except in cases of sensitiveness where the removal of the offending protein is followed by relief of asthma. It is clearly demonstrated that the best results are obtained when symptoms of asthma are relieved after the removal of the offending protein. These cases may continue indefinitely without symptoms, as shown by Cases XII and XIII, which fact is indisputable evidence of the specificity of the skin tests. Peptone evidently shows a higher percentage for cases of relief of asthma; autogenous vaccine and milk, a somewhat lower percentage than specific desensitization. But milk and vaccine show a higher percentage of cases of marked improvement than does specific therapy. The percentage of patients unimproved was somewhat higher with specific therapy than with vaccines or milk but lower than with peptone.

The results obtained with milk and peptone indicate distinctly that a non-specific element plays an important part in the desensitization. This deduction is further strengthened by the fact that a large percentage of cases show a positive skin reaction with the original protein after specific desensitization, where the patients were free from all symptoms for a considerable period of time. This phase of the study will be discussed in a subsequent report.

Non-specific Agents *vs.* Autogenous Vaccines in Cases of Non-sensitiveness. In comparing the results obtained with the use of milk and peptone as against autogenous vaccine, shown in Table II, one cannot help but note the marked difference between them. Walker, reporting a series of 75 non-sensitive patients treated with autogenous vaccines, showed 46.6 per cent relieved of asthma and 16 per cent improved. The results obtained in this series compare favorably, 46.4 per cent being relieved of asthma and 46.4 per cent markedly improved. Milk showed 75 per cent relieved of asthma and 12.5 per cent markedly improved; peptone, 62.5 per cent relieved of asthma and 27.5 per cent improved.

Auld,[10] using peptone intravenously and subcutaneously, observed that his cases could be divided into two main groups, showing no tendency to pass into each other. One group comprises patients who quickly respond to the treatment and in whom recurrences are less frequent and milder in character. The other group

is composed of resistant patients and is subdivisible into groups of totally resistant patients and those in whom, by careful immunization, the disease may be largely overcome. A similar experience was noted in this series. Some patients responded almost immediately, usually after the second or third dose, as show by Cases IX and X; others needed prolonged treatment, such as the patient in Case VIII, and some were resistant to continued treatment, such as those in Case VI. The exact observation was made with milk. However, patients failing to respond to milk, quickly respond to peptone and *vice versa* and others were resistant to both. This observation rather depreciates Peterson's[15] statement that peptone seems to be polyvalent for most of the substances causing anaphylaxis.

In comparison vaccines act in the same manner. When one fails a new vaccine obtained from the same source, but containing different organisms, will prove successful. Walker[16] attributes this fact to the isolation of the specific causal organisms. Some doubt is cast upon this interpretation, for the same phenomenon is noted with a change of non-specific agents. The explanation for this difference in the response to the various proteins can best be interpreted on the basis of Weichardt's[17] theory of "omnicellular plasma-activation."

The important factor in the use of non-specific proteins as a routine measure is the avoidance of anaphylaxis. This may be accomplished by testing for sensitiveness with the cutaneous test similar to the tests for sensitization. Properly carried out, this test should do away with the objection raised against the routine use of non-specific proteins.

Summary. 1. The cutaneous tests are undeniably specific and should be carried out in every case, for, as has been shown, where symptoms cease upon removal of the offending protein the best results are obtained.

2. A non-specific element enters largely into the benefits derived from specific desensitization.

3. The judicious use of non-specific proteins is a valuable adjunct to the treatment of bronchial asthma and should be used more or less as a routine procedure.

4. Milk is the non-specific agent of choice because of its ready supply and ease of preparation.

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THE DURATION AND MAGNITUDE OF THE HYPOGLYCEMIA AFTER INSULIN.

By Elmer L. Sevringhaus, M.D., Elizabeth Kirk

and

Harold J. Heath,

Madison, Wis.

(From the Laboratory of Physiological Chemistry, University of Wisconsin, Madison, Wisconsin.)

It has been recognized since the first published work of Banting and his collaborators[1] that the effect of insulin was of rather short duration. Recent work has shown[2] that in rabbits the extent of the reduction in the blood sugar does not follow closely the dose per kilo of body weight nor does it correspond to the actual level of blood sugar before the injection is made. The effect of a large dose of insulin is said to give a more prolonged reduction of the blood sugar than a smaller one, but the extent of reduction is not so much greater in the case of the larger dose as might be expected. In treating cases of diabetes with insulin it early became evident that we could not predict with any accuracy the amount of the

drug to be used in a given case to secure a definite reduction in the blood sugar level. The frequency of dosage necessary to keep diabetics without glycosuria was evidently variable. These clinical studies will be presented separately in a later paper. It is our purpose here to present studies of the effect of insulin on the blood sugar concentration of normal adults.

The subjects of these experiments were healthy students or members of the medical staff. The insulin used was in all cases "Iletin," supplied by Eli Lilly Company, whose coöperation is gratefully acknowledged. The dosage was in terms of the "unit" as marked on the vials of the drug. "The unit of iletin originally adopted was the amount required to lower the normal blood sugar of a 1 kilogram rabbit to 0.045 per cent." The dose was given as a single subcutaneous injection into the arm. Blood samples were taken from the antecubital veins, oxalated, and analyses begun at once by the method of Folin and Wu. During the period when blood samples were being taken the subjects were engaged in sedentary laboratory work, attending lectures, or passing from one room to another in the same building. None of the subjects had any food between the previous evening meal and the time of the last blood sample. The experiments were begun between 8 and 9 A.M. Four individuals were given 4 units each of insulin, Nos. 1, 2, 3 and 4. To Nos. 5 and 6 were given 8 units, and to Nos. 7 and 8 the maximum of 10 units. Fig. 1 shows the changes in the blood sugar level in these cases. The same sample of insulin was used for all these cases except No. 7. In the latter case a portion was used from a second lot of the drug of the same strength. The curves are marked with the body weights of the subjects in kilos. The intervals designated by S in the curves for Nos. 7 and 8 indicate the period during which there were symptoms referable to the insulin. In both cases symptoms began almost suddenly a few minutes after the second blood sample had been taken. In the first case symptoms were not expected. In the second the subject was skeptical as to the basis of the symptoms in the first case, but experienced very similar sensations. Both these subjects were members of the medical staff, and were accustomed to taking blood samples from each other in the fashion used here. Neither one feared in the least the consequences of a slight overdose, since they were familiar with the usual means of relief from such emergencies. There seems consequently little possibility of a psychic factor. The symptoms noted were a sense of trembling and poor muscle control. There was a feeling of weakness or exhaustion. The trembling was manifested by a slight, coarse tremor, but more particularly by inability to write a normal hand or to use a slide rule. There was no blurring of vision and no sweating. These symptoms were diminishing definitely in the second hour, and had disappeared entirely by the end of the third hour.

It is evident from the curves of Nos. 1 to 4 that the magnitude of the reduction of the blood sugar level is not the same in all cases. Neither does the effect seem parallel to the dose per unit of body weight. The blood sugar concentrations in cases 1, 2 and 4 were close before giving the insulin, *i.e.*, 79, 85 and 84 mg. per 100 cc. In the samples of blood drawn from one to one and one-half hours

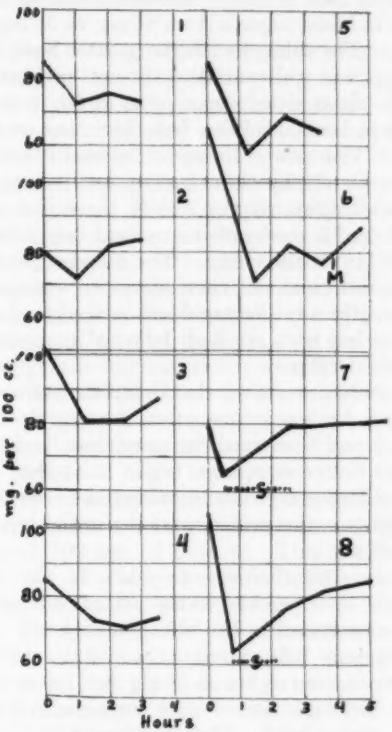

FIG. 1.—Blood sugar after injection of insulin.

4 UNITS EACH.		8 UNITS EACH.		10 UNITS EACH.	
1	59Kg	5	76Kg	7	82Kg
2	65Kg	6	63Kg	8	66Kg
3	68Kg				
4	74Kg				

after the injection, the values were strikingly close, 72, 73 and 72 mg.; but in No. 3 the initial level was higher, 101 mg., and the level was 80 mg. one and one-quarter hours later. This is a greater drop actually and relatively. Neither the actual decrease, the percentage decrease, nor the final blood sugar level seems uniform, nor related exactly to the dose per kilo.

The duration of the hypoglycemia is likewise variable. In No. 2 the original value is restored in two hours, in Nos. 1 and 4 the low levels are maintained at least three hours. In No. 3 the return to a normal level is not evident until after two and one-half hours. Both the smallest and the largest subject in the series show the slowest return toward a normal level.

In the 2 cases Nos. 5 and 6, where 8 units of insulin were the dose, the drop in blood sugar is from 84 mg. to 58 mg. and from 115 mg. to 70 mg. The subject with the greater body weight has the smaller change, but the variation is not proportional to body weights. The initial blood sugar value in No. 6 is higher than is usually found in normal adults, but there was no evident reason for this level. The return toward a normal blood sugar level is not shown completely by these curves, but it is evident that the process is not complete at the end of three and one-half hours. Subject No. 6 had a moderate noon meal beginning at the point indicated by "M" in the curve. The blood sugar about one-half hour after the meal had not risen above an average fasting level. There is apparently a rather rapid rise in the blood sugar after the minimum value has been reached, followed by a slower continued rise to the normal value.

The curve of No. 8 shows this delayed return to the normal level continuing for some time after the symptoms had abated. Both subjects 7 and 8 received the same dose, had the same blood sugar level just before symptoms began to appear, 65 and 64 mg. per 100 cc, and had symptoms for about the same length of time. The body weights varied widely and the initial blood sugar levels were 79 and 104 mg.

It seems impossible therefore to relate in any exact way the total dose or the dose per kilo to the actual or relative magnitude of the decrease produced in the blood sugar level. Nor can it be said that symptoms will appear at a definite blood sugar concentration. No. 5 went as low as 58 mg. per 100 cc with absolutely no symptoms, although Nos. 7 and 8 experienced trembling and weakness at a higher level. The duration of the hypoglycemia is likewise variable. Probably the larger doses cause a more lasting effect, but recovery is complete in No. 7 in two and one-half hours following 10 units, whereas it is incomplete in Nos. 1 and 4 after a longer period, although only 4 units had been injected. The impression from these curves is that the larger doses give greater reductions in blood sugar, tend to cause more prolonged effects, and that body weight has relatively a slight influence. These statements should be compared with the conclusions based on observations on insulin given to rabbits:[2] ". . . There is no contrast in the immediate results following injection of 0.3 and of 0.6 cc of the same preparation of insulin, which would indicate that so far as the initial rate of decline of blood sugar is concerned

a moderate dose has the same effect as an excessive one. The point of distinction between the moderate and excessive doses is more particularly with regard to the duration of their action." It is our impression that the extent of the decline of blood sugar is more striking than the duration of this reduced level. The curves shown in the article[2] referred to do not agree with the interpretation given. Both are admittedly variable, and are not subject to prediction.

Further evidence of the variable effect of insulin in the human body is presented in the study of the effect of the extract on the glucose tolerance curves of a number of normal subjects. These individuals were students who came to the laboratory without breakfast. A blood sample was taken, the dose of insulin given, and 100 gm. glucose given, dissolved in 200 cc water flavored with the juice of one lemon. Blood samples were taken at intervals during the morning, and urine samples were collected for the periods between the blood samples. The sugar content of the urine samples was determined by the method of Folin and Berglund.[3] During the period covered by the blood samples the subjects remained in the laboratory, seated most of the time. In some cases there was a slight sense of gastric distress, which was often relieved by drinking water about half an hour after the glucose was given. In each case a normal tolerance curve was determined on one day, and two or three days later the experiment was repeated with the use of insulin as indicated. The results are shown graphically in Figs. 2 and 3. If the normal curves are compared with each other, it is evident that there is no correlation between the body weight and the effect of 100 gm. of glucose. This corresponds to from 1.4 to 2.0 gm. per kilo body weight. But the three individuals whose tolerance curves are lowest, Nos. 13, 14 and 15, received 1.92, 1.90 and 1.67 gm. per kilo. The three whose curves extend the highest, Nos. 12, 17 and 19, received 1.43, 1.67 and 1.56 gm. per kilo. All these individuals must be considered normal. In no case did the urine sugar concentration reach 0.1 per cent, the concentration at which the clinical qualitative tests would have detected it. The highest points in these normal curves are in every case at either the half hour or one hour period after the ingestion of the sugar. Only within wide limits can the tolerance test be said to depend on the amount of sugar ingested per kilo weight. Besides the rate of absorption from the intestine, the nutritional state of the body with regard to glycogen must be an important factor. The body mechanism for the conversion of food glucose into the forms of carbohydrate which are used or stored in the body appears to operate better after a second portion of sugar than after the first ingested a very few hours previously.[4] Recent work[5] suggests that this mechanism may be the conversion of the alpha and beta glucose which is absorbed into the gamma form

for use in the oxidative and glycogenic functions of the body. This transformation is thought to be brought about by the liver and the pancreas together. The rate at which such a mechanism would become active at its optimum rate may well vary as do many other visceral functions even in the normal body. With so many variable factors it is too much to expect that an artificial condition

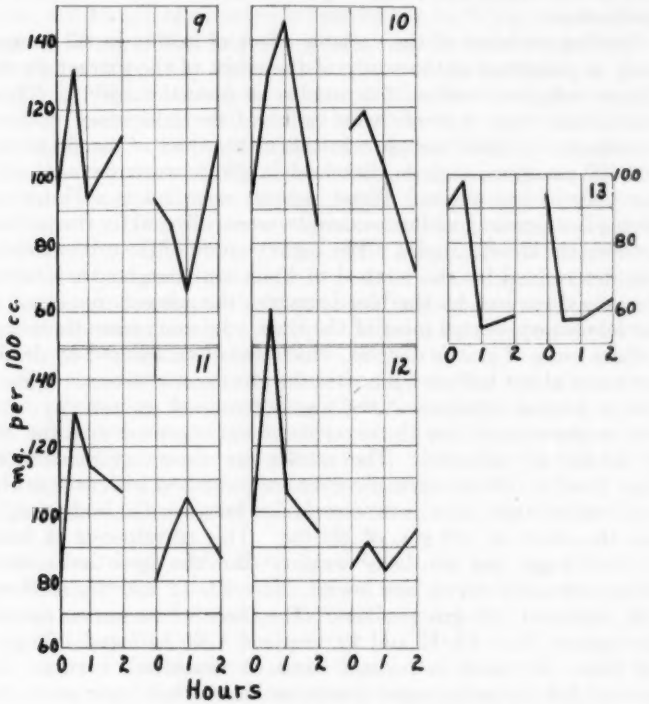

FIG. 2.—Glucose tolerance before and after insulin injection.

8 UNITS EACH.

9	54Kg
10	61Kg
11	70Kg
12	70Kg
13	60Kg

such as the feeding of 100 gm. of glucose would be followed by a uniform response in different individuals.

If now the tolerance curves after the administration of the insulin are compared with the normals, ten of the eleven individuals show a definitely lower curve due to the insulin. The extract is responsible for facilitating the removal from the blood of the

sugar being absorbed. But when the different curves are compared, as for example those of Nos. 9 to 13, all of which are from

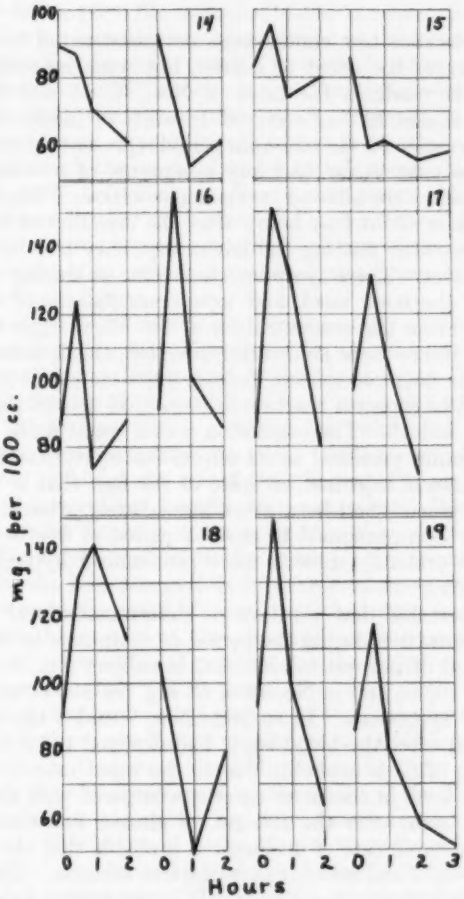

FIG. 3.—Glucose tolerance before and after insulin injection.

10 UNITS.		12 UNITS.		16 UNITS EACH.	
14	52Kg	15	53Kg	16	51Kg
				17	60Kg
				18	60Kg
				19	64Kg

subjects treated just alike, with 8 units of insulin, there is no constancy to the shape of the curve, to the maximum or minimum, and no constant relation to the curve from the same individual

without the use of insulin. The same may be said of Nos. 16 to 19, where 16 units was the dose. The tolerance test is not a physiological constant although it may be of real value in clinical diagnosis.

These tolerance test curves were not constructed to determine the duration of the effect of insulin, but some interesting observations were made in the cases of Nos. 16, 18 and 19. These three individuals, having received 16 units of insulin each, were under observation for the two-hour period represented by the curves. Since in no case so far had any symptoms of overdosage been observed they were allowed to return to classes. They reported later that just about four hours after the injection of the insulin, or two hours after leaving the laboratory, they had become very weak and faint. These symptoms had come on during or immediately after the noon meal, and were consequently of only short duration. From the concentration of the blood sugar in No. 19, 52 mg. per 100 cc three hours after injection, this is not surprising. But there is no more reason, *judging from the curves for the two-hour period*, to expect a reaction in Nos. 3, 16 and 18 than in Nos. 10, 13, 14, and 15. The conclusion which seems quite evident is that the insulin persisted in its effects for more than four hours from the time of injection, in spite of the fact that a "meal" of 100 gm. of glucose had been given immediately after it. If these curves had been continued to cover a period of five or six hours, they would probably show a more pronounced hypoglycemia in the later hours.

It is regrettable that we have no determinations of the blood sugar concentration during the period of symptoms in these cases. However it is of interest to note that in subject No. 18 a value of 49 mg. per 100 cc and in No. 19 of 52 mg. per 100 cc was reached *without* any symptoms. In subjects Nos. 7 and 8 the symptoms came on just after the blood sugar had dropped to 65 and 64 mg. per 100 cc. This is probably due to the rapid rate of decline in blood sugar level in the latter cases as compared with those where the decline came after the 100 gm. of glucose had been utilized. With such a rapid rate of decline it is probable that the curves as shown for Nos. 7 and 8 do not show the true minima. These values may be below 50 mg. per 100 cc. It is our feeling however that the reason for the variation in the level of blood sugar at which the first symptoms of overdosage become evident is an individual variation. We have observed in two diabetic men under treatment that when symptoms were observed the blood sugar concentration was between 60 mg. and 65 mg. per 100 cc in the one, and between 40 mg. and 50 mg. per 100 cc in the other. This was confirmed three times in 1 case and twice in the other.

The tolerance curves, both normal and after insulin, of Nos. 13, 14 and 15, are of different shape from the usual curve. The

absence of a significant rise of blood sugar after the ingestion of the glucose might be explained by a failure of the glucose to pass through the stomach.[6] But these curves show very definite declines one and two hours after the ingestion of the glucose. This hypoglycemia following a meal is as characteristic as the hyperglycemia on which attention is more usually focussed.[7] After the use of insulin in these 3 cases the change is that the hypoglycemia comes more rapidly and the slight peak which occurred in 2 of the curves before is now absent in all. May it be that these are individuals in which the mechanism for metabolizing glucose is so quickly and easily activated by glucose that venous blood never has a hyperglycemia after the ingestion of such a "meal"? Insulin seems to facilitate this process somewhat. These three individuals might be thought of as having unusually active pancreatic glands. Nos. 14 and 15 are sisters.

We have not added to the curves the urine sugar concentrations. In some cases there has been a tendency for the curve of the urine sugar concentration to follow that of the blood sugar. In others this has been directly the opposite. Closer inspection of the data shows that the real parallel is between the volume of the urine sample and the sugar concentration in it. With the small volumes often observed following the use of the 100 gm. of sugar in 200 cc syrup, the concentrations usually rose somewhat. Where there was diuresis, from drinking more water, the change was directly opposite. The concentration of the sugar in the urines of these different subjects was not uniformly decreased after the insulin. This inclines us to the point of view[7] that the sugars in the urine represent unusable sugars of the diet, and not the normal blood sugar escaping constantly, dependent on the blood sugar level. A slight glycuresis might well be found after such a tolerance test, using the juice of a lemon, and glucose of 99.4 per cent purity.

We feel that these results are of clinical importance in demonstrating that in the treatment of a diabetic the effect of a given dose of insulin can only be determined by the study of the blood sugar of that individual at intervals of not more than a few hours during a typical day. The choice of the particular times for taking blood samples with relation to meals and the dosage of insulin must be determined by experiment. The variable duration of the effects of insulin also make it important to know how long a given dose will show an effect in a certain diabetic, so that cumulative action may not be brought on with danger to the patient. Unless the patient is under careful control at all times, and the effect has been determined in his own case, it seems unwise to give two doses at less than six-hour intervals. The disadvantages of large doses given only once or twice daily in severe diabetics are apparent from the sudden reduction in blood sugar concentration which may follow in normals. We hope shortly to publish data from

the treatment and study of diabetics illustrating these points more in detail.

We have tried spraying insulin into the nostrils with an atomizer, but without effect. Ten units were given a rabbit on each of two days without any symptoms, and without a reduction of blood sugar. One of us took 10 units, another 20 units in a similar fashion, after fasting fourteen hours. There were no symptoms and no reduction of the blood sugar level.

Conclusions. 1. In normal human subjects the extent and the duration of the hypoglycemia after the injection of insulin are so variable that the result cannot be predicted from the dose per kilo of body weight.

2. The extent of the hypoglycemia and the duration of the low level are roughly parallel to the dose of insulin.

3. The depression of the sugar tolerance curves by insulin is not uniform in type or extent.

4. With increasing dosage of insulin both the extent and the duration of hypoglycemia are increased.

5. The blood sugar concentration at which symptoms of overdosage of insulin appear vary in different individuals in the region from 40 mg. to 65 mg. per 100 cc of blood.

6. The concentration of sugar in the urines of normal subjects does not follow the blood sugar level with or without insulin. It is related more closely to the urine volume.

7. The treatment of diabetics with small doses of insulin at intervals of not less than six hours is preferred to the use of larger doses at very long intervals, or of smaller doses at too short intervals.

8. Intranasal application of insulin is without effect.

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A REPORT OF SIXTY-FOUR CASES OF DIABETES MELLITUS TREATED WITH INSULIN.

By LEON JONAS, M.D.,

WOODWARD FELLOW IN PHYSIOLOGICAL CHEMISTRY, UNIVERSITY OF PENNSYLVANIA.

(From the Medical Division of the Hospital of the University of Pennsylvania and the William Pepper Laboratory of Clinical Medicine.)

THE great addition to our therapeutics given us by Banting[1] and his colleagues, namely, the insulin treatment of diabetes, is still so new that reports from the clinics where it is being employed are of value. On the medical service of the hospital of the University of Pennsylvania there have been treated 64 cases, and it seems desirable at this time to present certain observations made in connection with the insulin treatment of these cases.

The classification of the cases by age and severity is presented in Table I. The first group includes cases with no diacetic acid in the urine on admission. The second group includes cases with reduced CO_2 content of the plasma and with diacetic acid in the urine but with normal plasma PH. The third group includes cases with a lowered plasma PH in addition.

TABLE I.—NUMBER OF CASES ARRANGED ACCORDING TO AGE AND SEVERITY.

Age, years.	0–10	10–20	20–30	30–40	40–50	50	Total.
Mild	1	5	6	5	5	25 ++	47
Lowered alkali reserve	0	0	1	2	1	2	6
Lowered Alkali reserve low PH	0	2* +	3* +++	4* ++++	1*	1*	11
Total	1	7	10	11	7	28	64

\+ Associated acute infection.
* Coma.

The diets for the cases reported in this paper were prepared in a special kitchen under the supervision of an experienced dietitian. In the control of the treatment the following analyses were used: The hydrogen-ion concentration by the colorimetric method of Cullen;[2] urine ketones by the method of Van Slyke;[3] blood ketones by the method of Van Slyke and Fitz;[4] blood-sugar concentration by the method of Folin and Wu;[5] plasma CO_2 content and CO_2 capacity by the method of Van Slyke.[6] Most of the plasma CO_2 observations given in this paper represent content, but in a few

instances, indicated by an asterisk, the capacity is given. Acetone was determined qualitatively by the sodium nitroprusside test and diacetic acid by the ferric chloride reaction.

Treatment of Mild Cases. These patients were placed on a diet of 100 gm. of fat, 50 gm. of carbohydrate and 1 gram of protein for each kilo of body weight. If there was a glucosuria on this diet one dose of insulin, usually 5 units, was given twenty minutes before the noon meal. If a further increase was necessary a dose, usually 5 to 10 units, was given twenty minutes before breakfast and the same amount before supper. If necessary, larger doses were given before breakfast and supper or 10 units were given before each meal. When the urine became sugar- and ketone-free carbohydrate and fat were increased to furnish a maintenance diet. As the diet was increased the dosage of insulin was increased, if necessary, to prevent glucosuria and acetonuria and to maintain a fasting blood-sugar level between 0.12 and 0.15 per cent. The amount of fat allowed was within the limit of a ketogenic-antiketogenic ratio of 1.5 or less.

The insulin dosage of our mild cases varied from 5 units once a day to 30 units a day. We have observed in some patients that have been placed on a relatively liberal diet that the dosage of insulin must be increased at intervals to take care of the same quantity of food, even though there has been no gain in weight.

Treatment of Severe Cases. Seventeen patients showed a reduction of the CO_2 content of the blood below normal and the presence of a marked diacetic acid reaction in the urine, and 9 of these showed a reaction of the blood more acid than normal as determined by the PH of the plasma. Five of the 17 cases were admitted in coma. Eleven of the 17 cases were thrown into a critical condition by acute infections such as tonsillitis, pneumonia, upper respiratory infections or local pyogenic infections.

The treatment of these 17 patients varied with the degree of severity. If the patient showed a normal plasma PH the tolerance for carbohydrate was determined before insulin was given. If the patient showed a diacetic acid reaction in the urine and an acidosis as indicated by a lowering of the CO_2 content of the plasma and a fall in the plasma PH, a diet was given low in fat containing an amount of protein equal to 1 gm. per kilo of body weight and sufficient carbohydrate to safely balance the insulin, usually from 100 to 150 gm. per day. Ten to 15 units of insulin were given three times a day twenty minutes before each meal with, in some instances, a fourth dose at midnight. When the reaction of the blood became normal and the diacetic-acid reaction disappeared from the urine the insulin dosage and the diet were gradually adjusted until the patient could take if possible 800 to 1000 calories above the basal requirement and remain aglucosuric and free of ketones. The basal requirement was determined by the height-

weight formula of Du Bois.[7] The amount of fat to be given was calculated by the Woodyatt[8] formula so that the ketogenic-antiketogenic ratio should be 1.5 or below. The shift of the acid-base equilibrium in the cases treated with insulin is discussed in a paper by Cullen and Jonas.[9]

Case Reports. From the 17 severe cases the following typical ones are described in detail:

CASE I.—Ins. No. 22: M. W., a male, white, aged thirty-five years, Hungarian, was admitted to the medical division of the hospital, March 12, 1923. The symptoms of diabetes had been discovered a year before. As in so many cases the carbohydrate tolerance had been slightly below normal at the beginning, but gradually had become less until a marked restriction of carbohydrate was necessary to keep him aglucosuric. He had lost 30 pounds in the last year, and at the time of admission was weak. On admission his weight was 100 pounds, his height five feet five inches. There was no edema. The CO_2 content of the plasma was 38 volumes per cent; the PH of the plasma, 7.26; the blood-sugar concentration, 0.296 per cent. A twenty-four-hour collection of urine yielded 7.02 gm. of ketones in terms of acetone, 9.42 gm. of nitrogen and 112.5 gm. of glucose. The patient was placed on 50 gm. of protein, 20 gm. of fat and 100 gm. of carbohydrate per day and 10 units of insulin three times a day, twenty minutes before each meal. The third day after admission the CO_2 content of the plasma was 73 volumes per cent., PH 7.4 and the urine gave a negative diacetic acid reaction. On the fifth day the CO_2 content of the plasma rose to 81 volumes per cent and the PH to 7.46, the urine was alkaline and free of ketone. Bicarbonate of soda had not been given. The diet was then changed to 50 gm. of protein, 160 gm. of fat, 50 gm. of carbohydrate per day. The urine became sugar-free in a few days, and the fasting blood sugar fell to 0.142 per cent. The fat and carbohydrate were then gradually increased until the patient was taking 100 gm. of carbohydrate and 2400 calories per day. His basal requirement was calculated as 1410 calories. On the latter diet and 10 units of insulin before each meal, the urine remained sugar-free throughout the twenty-four hours, except occasionally during the night. He was discharged on April 21, 1923, in good condition. He weighed 114 pounds when discharged.

The other severe cases adequately treated with insulin responded equally well except that the gain in weight was not as marked as in the patient cited. This phase of the response to treatment will be discussed later. All of these patients on discharge were taking a maintenance diet with two or three doses of insulin, totaling not more than 30 units a day, were free from glucosuria, had a normal plasma CO_2 content and PH and showed no diacetic acid in the urine.

Cases of Coma. Previous to the use of insulin, patients in diabetic coma, with few exceptions, died. Cases of coma treated with insulin are now often rescued from death. When insulin becomes more generally used diabetic coma should become less frequent. In the treatment of coma the results from insulin are most spectacular.

Five cases of diabetic coma are included in this series. However, 2 patients died within an hour after admission. Therefore, only 3 of the cases were adequately treated with insulin and all of these recovered. Because of the unusual features the histories of 2 of these cases of coma are given in detail.

CASE II.—Ins. No. 5: M. I., white, female, American, aged thirty-four years, was admitted to the hospital, November 16, 1922. Two years before admission she began to have polydipsia and polyuria and gradually lost weight. On admission she weighed 91 pounds. She was untreated until November 12, 1922, when a physician was called to treat an acute gastro-intestinal attack. A diagnosis of diabetes was made and the patient immediately put on a restricted diet. On November 14, respiratory distress developed. On the evening of November 15 she became delirious and then stuporous. She was admitted to the hospital in the afternoon of November 16.

On admission she was in coma, from which she could not be aroused. There was marked respiratory distress. She was given intravenously 500 cc of a solution containing 5 per cent of glucose and 2.5 per cent of bicarbonate of soda. One hour later blood was taken from a vein at the elbow for analysis. The CO_2 capacity was 17 volumes per cent; the blood-sugar concentration, 0.411 per cent. The urine showed a marked glucosuria and ketonuria. After the venous puncture 20 units of insulin were given hypodermically. Within two hours she could be aroused. Ten units were given five hours later. Protocol No. 1 gives the progress of the case during the first fourteen days of her stay in the hospital.

The analysis of the protocol shows that relatively small doses of insulin may rescue a patient from coma. The shift of the acid-base equilibrium was most striking. In four days it passed to the alkaline side of normal. The urine was alkaline at the height of the shift. On the eighth day the plasma reaction again changed to the acid side of normal following a reduction in the dosage of insulin, because of an inadequate supply. After the dosage of insulin was increased the reaction passed in forty-eight hours to the alkaline side. The quantity of ketones in the blood fluctuated with the acid-base equilibrium.

On the morning of the tenth day the patient again became somewhat stuporous. There was no evidence, however, of Kussmaul breathing and analysis of the blood and urine showed a picture

PROTOCOL NO. 1.—CASE.—INS. NO. 5.

Day ending.	Diet per day.				24-hr. urine.				Plasma.		Blood.		Insulin units per day.
	Protein, gm.	Fat, gm.	Carbohydrates, gm.	Calories.	Glucose, gm.	Acetone.	Diacetic acid.	Total N, gm.	CO_2 volume, per cent.	Ps.	Ketones, gm. per liter.	Glucose, per cent.	
11–16	..	..	..	....	xx	xxx	xxx	....	*17	....	....	.411	32
17	..	..	..	....	6.8	xxx	xx	....	...	....	1.27	.265	32
18	..	..	..	....	....	....	...	....	†41	7.34	....	.313	32
19	..	..	..	....	20.0	xx	x	....	...	....	....	....	32
20	..	..	..	....	2.9	xxx	x	....	†66	7.50	.18	.200	24
21	41	31	32	476	26.4	8.42 gm.	...	5.92	...	....	....	....	16
22	45	31	29	559	40.2	xxx	xx	....	...	....	....	....	16
23	45	27	25	526	3.9	xxx	xxx	....	†29	7.24	.84	.174	32
24	43	14	34	460	tr.	x	0	....	†60	....	....	....	32
25	40	33	29	569	....	....	...	....	†73	7.48	....	0.35	32
26	41	27	60	672	5.7	0	0	....	...	....	....	....	32
27	46	28	81	797	4.9	x	0	4.20	...	....	....	....	32
28	48	29	88	832	tr.	x	0	....	...	....	....	.094	32
29	53	73	85	1239	....	....	...	....	†71	7.54	....	....	32

* = capacity. † = content. xxx = strong reaction. xx = moderate reaction. x = weak reaction.

quite different from that of coma. Urine obtained by catheterization showed no sugar or ketone. The blood-sugar concentration was 0.035 per cent. About 25 gm. of glucose were given at once, and she recovered in a few minutes from the stupor. When discharged, December 22, 1922, she was receiving 8 units of insulin before each meal with 80 gm. of carbohydrate per day and remaining aglucosuric and free of ketone. At the present time, seven months after discharge, on 10 units of insulin twice a day, before breakfast and supper, she is able to carry on her household duties.

CASE III.—Ins. No. 11: T. C., male, white, American, aged eighteen years, was admitted to the ward, February 11, 1923. The onset of diabetes was in February, 1921, after an attack of mumps. With the exception of a few weeks of hospital treatment in July, 1921, he had been untreated. On February 6, 1923, he developed acute tonsillitis, which rapidly brought about the present crisis. On admission, it was difficult to arouse him. He presented a classic picture of severe diabetes. Air-hunger was marked. Examination of the urine showed sugar and much diacetic acid. Protocol No. 2 presents his progress during the first six days in the hospital.

The outstanding features of his case are the plasma PH 6.98, which up to this time is the lowest, we believe, recorded with recovery, and the rapid shift of the acid-base equilibrium from markedly increased acidity to the alkaline side of normal. At the outset 10 units of insulin were given every six hours. After two days the dosage was reduced to 30 units per day.

On March 19, because of a break in diet, acidosis developed. The PH of the plasma passed to 7.22 and the CO_2 content to 38 volumes per cent. Ten units of insulin, every sixth hour for three days, restored his acid-base equilibrium to normal. He was discharged from the hospital, May 21, 1923, sugar-free and ketone-free, on 10 units of insulin three times a day with 80 gm. of carbohydrate per day and a total caloric intake per day of 1700 calories.

It is of interest to compare these relatively small doses of insulin with the massive doses used in some other clinics in the treatment of coma. It is possible, of course, that the dosage described above would not prove adequate for the treatment of all cases of coma.

Bicarbonate of soda was not given to these cases because we desired to follow the shift of the acid-base equilibrium in severe acidosis treated with insulin and without alkali therapy. As a routine, we had been accustomed to give bicarbonate of soda to cases of diabetic coma. Cases of acidosis not in coma have not been given alkali because when insulin is used the acid-base equilibrium rapidly becomes normal.

Diabetes with Intercurrent Infections. Intercurrent infections either mild or severe usually cause a reduction of the carbohydrate

PROTOCOL NO. 2.—CASE.—INS. NO. 11.

Day ending.	Diet per day.				24-hr. urine.			Plasma.			Blood.		Insulin units per day.
	Protein, gm.	Fat, gm.	Carbohydrates, gm.	Calories.	Glucose, gm.	Acetone.	Diacetic acid.	Total N, gm.	CO_2 volume, per cent.	PH.	Ketones, gm per liter.	Glucose, per cent.	
2–12	28	8	269	1266	120	xxx	xxx	18.5	*16	*6.98	*.370	*.326	30 } 10 units
13	27	14	122	733	29	xx	0	....	44	7.32	.110	.306	40 } every 6
14	35	18	147	904	84	xx	0	10.4	64	7.51	.074	.153	40 } hours.
15	42	16	99	720	36	xx	0	....	58	7.42	.....	.....	30 } 10 units
16	39	20	39	498	8	x	0	8.12	58	7.43	.....	.190	30 } before
17	47	20	79	702	tr.	x	0	....	....	.....	.....	.....	30 } each meal.

* = before insulin. xxx = strong reaction. xx = moderate reaction. x = trace.

tolerance, and in many instances have led to coma and death. Surgery on diabetic patients has been especially dangerous because of the high mortality among operated patients. Six of our cases exhibited intercurrent infection, 4 of the 6 being cases of diabetic gangrene, 1 a patient with carbuncles and another with lobar pneumonia. Insulin diminishes the seriousness in these cases. Its efficacy in the control of diabetes during acute infections was striking in all 6.

The Effects of Insulin on Blood-sugar Concentration. Early in our experience with insulin we observed a mild insulin reaction, weakness and sweating in the afternoon, in spite of the presence of glucose in the twenty-four-hour collection of urine and a hyperglycemia in the morning before injecting insulin.

The following studies were, accordingly, made. Blood-sugar concentration was determined, beginning before the first dose of insulin for the day and continuing at intervals until 9 or 10 o'clock at night. Specimens of blood were taken every hour, or hour and a half, and immediately before each insulin dose and just before taking food. A specimen of urine was collected, when possible, immediately after each venous puncture and examined for sugar, acetone and diacetic acid.

The results of four such experiments are plotted in the charts. The amount of carbohydrate and the dosage of insulin together with the time of administration are represented by columns, solid for insulin, hatched for carbohydrate; the scale of plotting for the insulin and carbohydrate is so chosen that columns of equal height indicate insulin and carbohydrate in the ratio of 1 unit of insulin for 2 gm. of carbohydrate. This is the ratio which Campbell and Fletcher[10] give as a balancing ratio in suitable cases. The patient whose curve is represented in Chart I received no carbohydrate for breakfast, 36 gm. at noon, 23 gm. at supper and 5 units of insulin before breakfast and supper and 10 units at noon.

The patient whose curve is shown in Chart II received no carbohydrate for breakfast, 46 gm. at noon and 23 gm. at supper, and 5 units of insulin before breakfast and supper and 10 units at noon.

The patient whose curve is shown in Chart III received no carbohydrate for breakfast, 41 gm. at noon and 33 gm. at supper and 10 units of insulin before each meal. This patient, on this regimen, had been aglucosuric and free of ketone two days before this experiment. The cause of the sudden ketonuria and glucosuria is probably that the patient, who was somewhat unreliable, had taken unauthorized food the day before the experiment. Two days later on the same regime diacetic acid was not present in the urine and only a trace of sugar.

The patient whose curve is shown in Chart IV received 80 gm. of carbohydrate per day and 10 units insulin before each meal. Her twenty-four-hour collection of urine had a trace of sugar.

Her curve illustrates well the morning hyperglycemia. Food was last taken at 6 P.M. At 8.30 P.M. there was a slight insulin reaction with hypoglycemia. The next morning there was marked hyperglycemia.

The patients whose curves are plotted in Charts I and II, respectively, received 5 units of insulin before breakfast and supper and 10 units at noon. The largest dose of insulin was given at noon because that meal contained the largest portion of carbohydrate.

The hypoglycemia shown in Chart I accounts for the mild insulin reaction observed in this patient in the afternoon.

Inspection of the charts shows a drop in the blood-sugar concentration during the day and a rise during the night. The minimum value occurred in the afternoon or early evening and coincided with the time at which hypoglycemic reactions, characterized by weakness, sweating and headaches, had been noted in patients receiving similar insulin treatment.

In explanation of the time relations shown in these curves it is possible that we are dealing during the afternoon with an accumulation of insulin from both morning and midday doses. It is possible also that there is a delay in the response of the blood-sugar curve to the ordinary complex-carbohydrates of the diet, due to the time consumed in digestion and absorption. It would seem that such delayed response to carbohydrate ingestion is the important factor in the first three charts. Approximately one hundred and eighty minutes elapsed before the carbohydrate of the food influenced the blood-sugar concentration in these cases. This contrasts sharply with the prompt effect of administering pure glucose by mouth, as was done in Case Ins. No. 5 for the relief of the symptoms of hypoglycemia. In Chart IV both the accumulating effect of the insulin and the delayed response to the carbohydrate of the meals are apparent.

These observations suggest that the amount of insulin sufficient to balance the carbohydrate of the meal, might to advantage be given at a time interval after the meal rather than before it. It is possible that such a regimen would lead to a more even blood-sugar regulation and avoid the symptoms of hypoglycemia as well as the night hyperglycemia and glucosuria.

The promptness with which symptoms of insulin hypoglycemia develop when the balancing carbohydrate is not provided, is strikingly illustrated by one of our cases. A child, aged three years, had been admitted because of diabetes. Her urine was ketone-free. She was in a fair state of nutrition. On 5 units of insulin, before each meal, and 35 gm. of carbohydrates per day her twenty-four-hour collection of urine was seldom entirely free of glucose. This diet consisted of eggs, chicken, butter and 5 per cent and 10 per cent vegetables. On a certain day, although her condition had seemed satisfactory, an hour after supper she suddenly

had convulsions, which were tonic and clonic and lasted eight minutes. Shortly after the convulsions she vomited. The vomitus contained most of the food taken at the noon meal and nearly all of her evening meal. Following the vomiting she became stuporous. The blood-sugar concentration at this time was 0.03 per

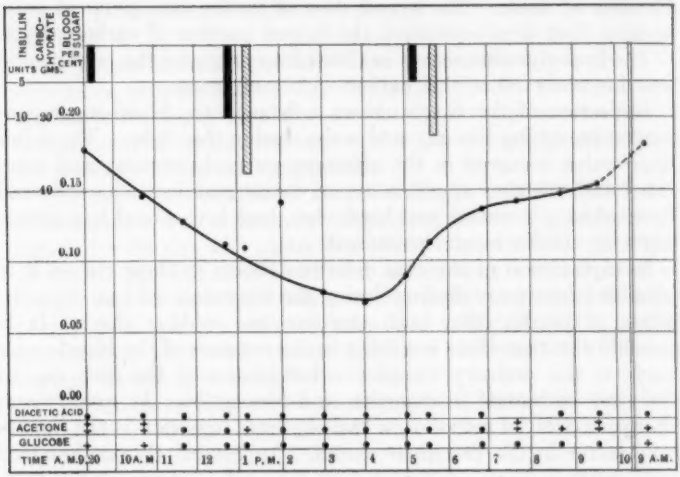

CHART I.

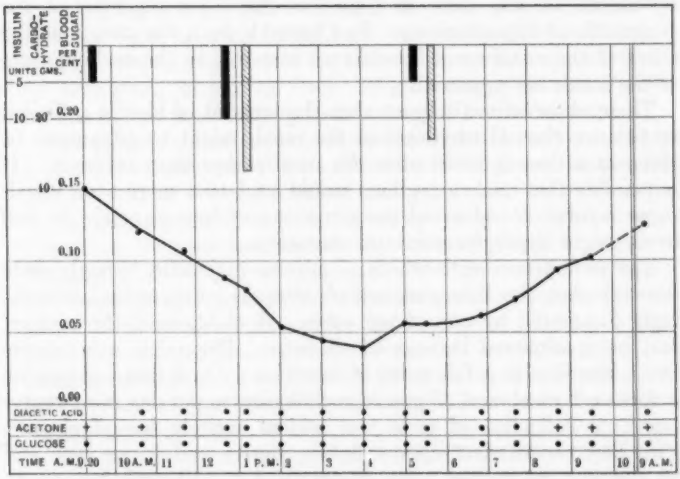

CHART II.

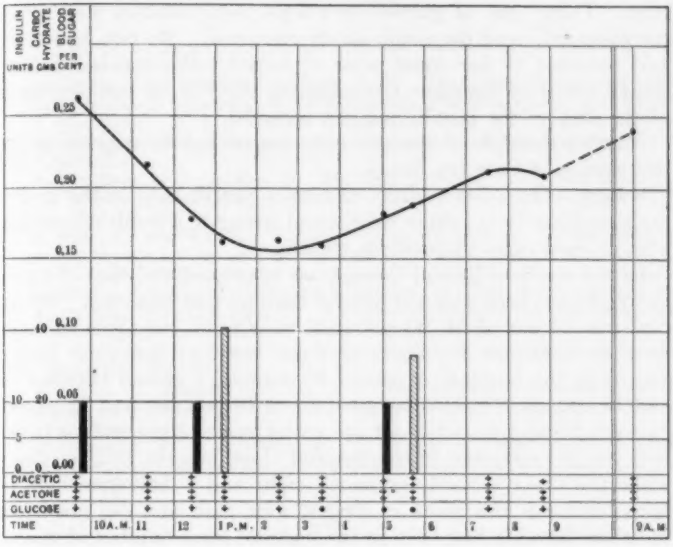

CHART III.

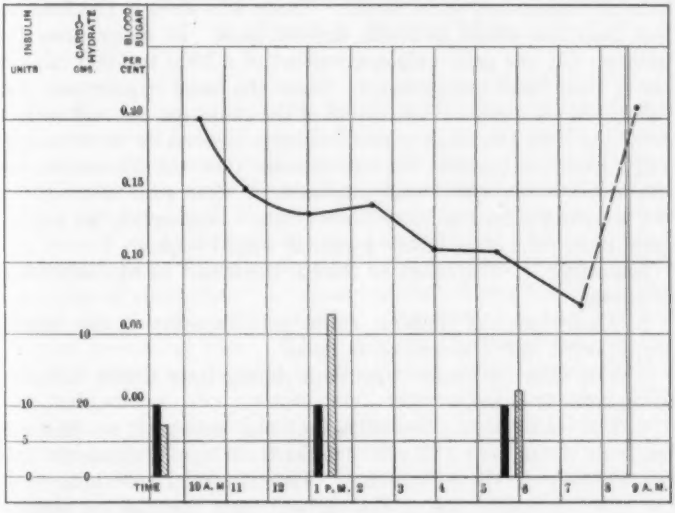

CHART IV.

Curve: blood-sugar concentration; Solid columns: insulin dosage; Hatched columns: carbohydrate in food.

Diacetic acid, acetone and glucose: qualitative reaction in twenty-four-hour urine: • = none; + = slight; ‡ = marked.

cent. Thirty gm. of glucose in a 5 per cent solution were given intravenously and the child slowly recovered. In two hours she had returned to her usual state of health. We concluded that, due to failure of digestion, the balancing effect of the carbohydrates of the diet on the insulin had not occurred.

Another example of hypoglycemic stupor has been given in the description of Case Ins. No. 5.

Weight. One of the effects of insulin particularly in the undernourished has been gain in weight and strength, a result not attainable in most cases by previous methods.

In our study of insulin therapy we have observed that the gain in weight has been a slower process than we had expected. Of our patients, 34 out of 64 did not gain weight; 27 out of 64 patients were at discharge 2 pounds or more heavier than their lowest weight in the hospital; 2 gained 20 pounds, 4 gained between 10 and 15 pounds; 9 gained between 5 and 10 pounds; and 12 gained between 2 and 5 pounds. Of the 2 who gained 20 pounds, 1 (Case Ins. No. 11) remained in the hospital three months and ten days, while the other (Ins. 4) remained eight and a half months. In both instances the gains in weight were slow and did not begin until the patients had been in the hospital for a number of weeks. Those gaining from 10 to 15 pounds were in the hospital from five weeks to two months. The minimum stay for those gaining 5 to 10 pounds was three weeks. Those who were in the hospital less than two weeks as a rule did not gain. In many cases the patients did not gain weight on a diet of a 1000 to 1200 calories above their basal requirements. Since the basal requirement was calculated for a normal individual of the same age, sex and surface area, and since the plane of metabolism is lowered by loss of weight and dietary restriction one can assume that the allowance was liberal for a diabetic. Our conclusion is that gain of weight is not immediate even on very liberal diets. Apparently an adjustment must take place before a gain in weight begins.

Summary. 1. The effect of insulin treatment in 64 diabetics is discussed.

2. Three cases of diabetic coma with recovery under insulin are reported and 2 described in detail.

3. The value of insulin treatment during intercurrent infection in diabetes is noted.

4. The blood-sugar concentration was measured at frequent intervals throughout a day in 4 patients on insulin treatment and the resulting curves constructed. The time relations apparent in the effect of insulin and of the carbohydrate feedings are charted and certain implications as to the timing of the insulin dosage are discussed.

5. A delayed gain of weight on insulin therapy is noted.

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THE TREATMENT OF DIABETIC COMA WITH INSULIN.*

By Nellis B. Foster, M.D.,
NEW YORK.

Until the last year it has not been my good fortune to see a recovery from diabetic coma. There are reports in the literature it is true, that recovery has taken place, but with possibly one or two exceptions, coma quite promptly recurred and led to death. Since October, 1922, 15 cases of diabetic coma have been treated; of these 8 recovered from the coma and of these 8 who recovered, 5 are still alive. These cases were treated within insulin. Having a means of controlling the primary acidosis factor in coma, we have been able also to study secondary, contributory factors and devise means to combat them. There seems to be three abnormal conditions which are notable in all cases of diabetic coma; acidosis, desiccation of the tissues, and myocardial weakness. While acidosis is primary and in a sense probably initiates other disorders in the body-chemistry, it is also true that death may result from one or both of the secondary factors after the acidosis has been corrected. Some years ago when the causation of diabetic coma was still uncertain, Magnus-Levy asserted that the theory of

* Read as part of a symposium on insulin treatment at the meeting of the Association of American Physicians.

death from acidosis must be accepted unless treatment with alkalies had been successful to the degree of rendering the urine alkaline. We no longer measure degrees of acidosis by urine examinations, but death may occur in diabetic coma after the blood no longer gives evidence of acidosis and there are now several reports of death in diabetic coma after the urine had become alkaline. I have seen one such case. Therefore I wish to emphasize that other factors than acidosis demand attention in the treatment of diabetic coma and that they cannot be neglected.

Everyone who has seen cases of diabetic coma must have been impressed by the evidence of desiccation of the tissues. Although there may be no fever, the mouth and pharynx are invariably dry and parched to a degree usually seen only in febrile disease. The reduced intraocular tension is also probably an effect from water loss. As a matter of fact, every case of severe diabetes presents evidence of the difficulty of maintaining the water balance in the body. Now, as acidosis becomes more and more severe two conditions develop which prevent the patient from drinking adequate amounts of fluid. He is often nauseated; sometimes he vomits and although the thirst be agonizing he fears to drink, or vomits when he does drink. In the course of hours he becomes drowsy and drinks less and less as stupor creeps on him. In brief, less water is taken into the body as acidosis progresses. But during this period the water elimination does not decrease. The glucose excretion is extreme and persistent and constantly abstracts water from the tissues for urine formation. Pulmonary ventilation is increased and augments the water loss of the expired air. Even the small amount of endogenous water is diminished, since both carbohydrate and fat, which normally are burned to carbon dioxide and water, now are not oxidized (glucose), or are oxidized only to intermediate ketone bodies. A moment's thought on these abnormal conditions clarifies the extreme desiccation which is notable in cases of diabetic coma. The significance of desiccation alone as a cause for abnormal metabolic states was demonstrated in the classical experiments of Woodyatt.

It has been recognized for years that when fluids are injected intravenously in cases of diabetic coma an especial care must be exercised or death may suddenly occur. The fluid must be given more slowly than is necessary in other diseases, and the amount injected at one time must be small. It is a general belief, I think, that the myocardium in diabetic acidosis is seriously damaged and must be protected. The hearts of young subjects examined at autopsy, show hypertrophy and cloudy swelling of the muscle. During life there is usually tachycardia, and occasionally delirium cordis. On one occasion it happened that a patient came out of coma and conversed about his disease and then developed symptoms which seemed typical of acute cardiac failure and died. There

is nothing definite and little is known of the vascular mechanism in severe acidosis. But until we possess a better understanding it seems wise to use the general measures employed when a similar train of signs is presented.

There is no means of determining in an individual case the amount of insulin which will be required to stop the formation of ketone bodies. The smallest amount effective in my series was 70 units given in a period of six hours, and the largest dosage used in a case that recovered was 180 units during twelve hours. In the beginning our dosage was too small because we had to economize in insulin. Now we are more liberal. In such a critical condition the best rule is to be sure that one uses enough. The first dose may be 25 units at least, in adults, and repeated smaller doses at intervals of an hour or two. The urine should be tested for sugar every two or three hours and heavy dosage is advisable, so long as large amounts of sugar are excreted. When the sugar in the urine begins to fall, then the dosage of insulin can be decreased and the interval between doses lengthened. It is evident from numerous observations, both in coma and severe acidosis, that the blood sugar is most variable and apparently has no clear relation to the clinical symptoms. The concentration may be as low as 250 mg. per cent, a not uncommon figure in many cases in good condition and free from ketonuria. Then, too, it has been observed that the blood sugar may be higher after the patient has recovered from coma than it was during coma. This is probably due to the glucose given in the rectal instillations.

That adequate amounts of glucose be available in the tissues seems to me important. Acidosis is initiated by failure of the oxidation of glucose. Progressively, then, fat and protein are substituted as sources of energy. The glucose from protein not being utilized, the metabolism of fat is progressively imperfect. The primary object in treatment is to substitute a carbohydrate metabolism for a dominant fat metabolism. Insulin makes it possible to accomplish this end but only when glucose is available for oxidation after insulin is given. Therefore, it is logical, in our opinion, to use glucose in clysters and in beverages. For the latter, orange juice is satisfactory and gratefully taken.*

The use of alkalies in severe acidosis has been a debated subject. On purely theoretical grounds, there is ample basis for the administration of large doses of bicarbonate of soda. Underhill's experiments some years ago suggested that more sugar was utilized when alkalies were administered and Mosenthal has recently applied this principle to human subjects. During coma little liquid can be given by mouth and the amount of alkaline salts which can be

* For rectal instillations Karo syrup is an available source of glucose. Two ounces to the pint of water makes a solution of approximately five per cent strength. Only pure dextrose may be used intravenously.

given intravenously is insignificant. We have used 3 per cent bicarbonate of soda solution along with glucose for rectal instillations and by the Murphy drip method. Any good effect of the alkali, *per se*, is obscured because of several measures employed simultaneously. Physiological saline solution has been used for hypodermic and intraperitoneal injections and 3 per cent sodium bicarbonate solution intravenously.

The variation in procedures in different cases is shown in the summaries of clinical records. The direct aims in our methods have been to arrest ketone formation by restoring an adequate oxidation of glucose; to relieve desiccation by introducing water into the body through every avenue of absorption; and finally to support, or stimulate the circulation by digitalis and caffein.

CASE I.—Y. P., aged forty-eight years, was admitted to the private patients' building, October 4, 1922. She had had diabetes five years and a week before developed infection of her ring finger following the prick of a pin. Operation was performed October 4, 1922 (Dr. Hitzrot) and her left ring finger amputated with removal of the metacarpal bone; the flexor tendons were gangrenous and the wound was left open. Culture showed Staphylococcus aureus. October 7, the urine contained 2.7 per cent of sugar and was strongly positive for acetone. The blood sugar was 0.364 per cent. The patient was in profound coma. Murphy drip was started and 30 cc of iletin given during next six hours. She died at 6 P.M. This patient was a mild diabetic, her disease was temporarily severe and acidosis was initiated by infection. Had we had sufficient iletin we believe her life could have been saved.

CASE II.—G. H., aged sixteen years, had been a patient in the Methodist Episcopal Hospital in Brooklyn for a month before transfer to the New York Hospital. He was admitted in coma, October 3, 1922. Prior to transfer he had received 30 units of iletin. The typical signs of diabetic acidosis were present. The blood CO_2 was 9.9 volume per cent, and the sugar 260 mg. During the first twelve hours this patient received 100 units of iletin and another 100 units during the following eighteen hours. Fluids were given by rectum at first, and as soon as the patient roused sufficiently by mouth also. The patient became conscious and rational about fourteen hours after treatment commenced. His food at first was 1 liter of milk per day with orange juice, later a measured diet. Recovery was perfect and he was discharged in November. He was faithful in executing directions and gained 10 pounds in weight on continued iletin treatment of 15 to 20 units per day. In February he contracted influenza and died, whether in coma, or not we do not know.

CASE III.—A. D., a woman, aged forty-seven years, who had had diabetes for an indefinite period. On account of diabetic gangrene, her left leg had been amputated just below the knee. Sugar had been eliminated from the urine before operation. The operation was followed by a fibrile reaction and sugar reappeared in the urine. December 26, 1922, two days after the operation, the patient was stuporous and had a temperature of 101° F.; her blood sugar was 0.3 per cent; urinary sugar approximately 2 per cent, and acetone was present. By the use of 50 units of iletin in the next twenty-four hours urinary sugar was reduced to a trace and the blood sugar reduced to 0.17 per cent. The blood CO_2 was raised from 20 to 40 per cent. On the appearance of gas bacillus infection in the wound, iletin treatment was abandoned.

CASE IV.—J. C., aged twenty-one years, gave a six-day history of extreme polydypsia and polyuria. Thirty-six hours previous to admission he felt very weak and faint. Twelve hours previous to admission he seemed to be somewhat delirious and six hours later became comatose and remained so until he was brought to the hospital. Examination of the urine by his doctor had shown sugar of 4 per cent but no acetone or diacetic acid. No albumin or casts were present. The patient was told he had diabetes and was referred to the hospital. Past history revealed that he had gained weight from 140 pounds to 230 pounds, his present weight, in the course of the last three years. His father and mother were both rather obese but not particularly large.

Physical examination showed a very obese young man with flushed skin in deep coma. His respirations were 55 per minute and the pulse rate 120. There was suggestive acetone odor on his breath. The heart sounds were very distant and the second sound was scarcely audible. His blood-pressure was 86/56. Examination of the eye grounds disclosed nothing abnormal. A diagnosis of diabetic coma was made and the patient was treated with iletin injections and Murphy drip of 2 per cent glucose and 2 per cent sodium bicarbonate. As the heart was evidently failing he was given 4 ampules of digifolin subcutaneously. The patient did not recover consciousness but died after eight hours, having developed edema of the lungs. Immediately after death the bladder was catheterized but only 25 cc of urine was obtained. *This showed sugar and a faint trace of acetone.* Nothing abnormal was found in the postmortem examination. Blood taken four hours after death had a sugar content of 1.058 per cent. Non-hemolytic streptococci were grown from the blood culture.

CASE V.—Mrs. N. S., aged twenty-eight years, developed diabetic coma December 9. She had had diabetes about a year and had failed in health rapidly. Her treatment in the past seemed to

have been rather indefinite. On December 8 and 9, she had felt sick and the bowels had not moved for several days. The patient was emaciated, weighing 85 pounds. The face was flushed and the respirations were characteristic of acidosis. She was not in deep coma but could be roused, not, however, sufficiently to answer questions. The blood sugar was 450 mg. per cent and the CO_2 13 volume per cent. The routine method of treatment was used and 5 units of iletin were given every two hours. As soon as the patient was sufficiently conscious, a matter of six hours, she received milk and orange juice. On December 13, the total glucose tolerance was determined to be 60 gm. (including glucose, from protein, determined on the basis of urinary nitrogen). A diet containing 1000 calories was ordered and with 10 units of iletin daily the patient maintained a sugar-free urine and was sent home December 22, weighing 89 pounds.

CASE VI.—S. B., aged thirty-six years, was transferred from Bellevue Hospital to New York Hospital January 1, 1923. The patient was unable to speak any language familiar to the staff and the only history was of severe diabetes recognized at Bellevue. He was admitted in deep coma although he had had 50 units of iletin during the six hours before his transfer. The usual routine treatment was carried out and 5 units of iletin were given every two hours. The patient recovered from coma in about ten hours. As soon as consciousness returned the patient commenced to vomit and this continued at short intervals. Examination revealed signs suggesting acute dilatation of the stomach. This was treated by gastric lavage and no fluids were given by mouth. In spite of this obstacle the patient continued to improve and the urine was free of sugar on the fourth day. He left the hospital against advice, but has only recently returned to Bellevue for treatment (April).

CASE VII.—D. G., aged fifty-one years, had had diabetes of a mild type for a number of years. In the latter part of December he took cold which resulted in bronchitis and then pneumonia. He became stuporous during the day of January 2 and was in coma when seen January 3. Samples of blood were not secured at the first examination. He was given 5 units of iletin every three hours. Consciousness returned in ten hours and the blood sugar was then 0.306 per cent and the CO_2 32 volume per cent. The iletin dosage was decreased and everything progressed favorably for a week. We then ran out of iletin and this patient had none for five days. His diet at the time iletin was discontinued contained 1400 calories. It was reduced to 770 calories (P. 40, C. 40, F. 50). The blood sugar was then 0.174 per cent. On the sixth day coma developed a second time and having received a new stock of iletin 25 units

were given in one dose and 10 units every two hours. Consciousness returned completely after about twelve hours.

The patient died January 23, of pulmonary abscess.

CASE VIII.—M. L., aged six years, was admitted February 6, 1923, with a history of diabetes of three years' duration. The child became drowsy about twenty-four hours before admission to the hospital. The temperature was 99.8° F., pulse 135, respirations 40. The patient was drowsy and the tongue and pharynx were dry. The reflexes were present but sluggish. She was able to swallow and orange juice and water were given. Glucose in a 5 per cent solution was administered by Murphy drip and 200 cc was absorbed in the first six hours. The first dose of iletin was 25 units and three hours later 10 units; 70 units were given in all in the first fifteen hours. The urine then contained no sugar and the blood sugar was found to be 0.047 per cent. There were no signs of shock but iletin was discontinued temporarily. For the first two days milk alone was given and then a standard diet. This patient is receiving 12 units of iletin per day which enables her to utilize a diet of 1100 calories. She has gained in weight and her condition is satisfactory.

CASE IX.—H. W., male, aged twenty-eight years, was admitted to private pavillion, February 6, 1923. He was said to have had diabetes two years. For four days he had complained of headache, anorexia, nausea, and constipation. On the morning of February 6, he was given a colonic irrigation at 11 A.M. and became stuporous an hour later. At 6 P.M. the temperature was 101° F., pulse 112, and respirations 32. The patient was deeply comatose with typical respiration, soft eyeballs, immobile pupils and absent reflexes. Treatment consisted of soda bicarbonate solution intravenously and 5 per cent glucose by the Murphy drip method, black coffee by gavage and iletin. During three hours from 6.30 to 9 P.M., 90 units of iletin were given. Death occurred at 9.15 P.M. The blood taken just after death contained 0.375 per cent sugar.

CASE X.—Patient M. Z., aged thirty-three years, was admitted to the Second Division, New York Hospital, February 8, 1923, in the morning, in diabetic coma. The urine showed sugar, blood chemistry was not done. She was given an initial dose of 25 units of iletin and following that was given 10 units every three hours. A rectal instillation of sodium bicarbonate and glucose was given every four hours. The patient did not come out of coma and died the night of admission. She had been ill for only six months and there was a rapid increase of symptoms during the last week before admission. During the ten hours in the hospital she received 45 units of iletin. She had been in coma about six hours before admis-

sion and the duration of the coma was about fifteen hours. This patient received only 45 units of iletin, probably an inadequate amount.

CASE XI.—Patient L. T., aged twenty-six years, had been treated under Banting in Toronto in October, 1922. Iletin had been abandoned in January, and the patient had eaten freely. He was admitted to Lincoln Hospital in coma February 26, 1923, at 9.30 P.M., and was treated by my assistant, H. J. Spencer. The temperature was normal, pulse 150 +. The patient was emaciated and breathing in a typical way; the pupils were small and sluggish and the reflexes absent. Treatment consisted in the routine measures to relieve desiccation, and iletin. Seventy units were given in the first six hours and the patient became conscious and rational. The blood sugar was 0.395 per cent on admission and rose to 0.638 per cent at the end of twenty-four hours. Improvement was continued and the urine was free of ketones on the third day after admission. On a diet of P. 45, C. 52, F. 65, with 20 units of iletin per day, the sugar disappeared from the urine. Indefinite pulmonary signs led to roentgen-ray examination which suggested a resolving pneumonia. This patient is alive and doing well.

CASE XII.—Mrs. E. S., aged fifty-six years, developed diabetic coma February 28, 1923. She had had diabetes some seven years. The disease had caused little inconvenience until about six months ago. Since then there has been a rapid loss in weight and she has become too weak to leave her bed. The diet has been of the usual indefinite type and the urine, according to reports from commercial laboratories, had contained 3 to 6 per cent of sugar, also ketone bodies.

The patient was a small, very emaciated woman. Her face was sallow, slightly flushed and the respirations were rapid and deep. She was semi-comatose. The temperature was 96° F., pulse 100, respirations 30. The pupils reacted slightly, but other reflexes could not be elicited. The intraocular tension felt decreased. The blood sugar was 535 mg. per cent and the CO_2 11 volume per cent. Treatment consisted of an enema followed by a 10 per cent glucose and 4 per cent soda bicarbonate instillation by means of the Murphy drip method. Twenty-five units of iletin were given at once and 10 units every two hours till the urine was free of sugar. This occurred at 8 P.M., March 1. The patient became conscious about fourteen hours after treatment was commenced. March 2, the blood sugar was 136 mg. per cent. From March 1 to 7 the diet consisted of 1 liter of milk and the juice of twelve oranges per day, 60 to 80 units of iletin were given daily in doses of 10 units each. March 7, the diet prescribed was P. 100, C. 150, F. 210; and this was changed March 13 to P. 70, C. 160, F. 100. She

was now receiving 40 units of iletin per day and sugar disappeared finally from the urine March 17. The patient was sent home March 20, having gained 10 pounds. The blood sugar ranged from 135 to 145 mg. per cent and the urine was free of sugar and ketones. Her present diet is P. 70, C. 100, F. 160; and 40 units of iletin per day is taken in two doses. Her condition is satisfactory.

The next case was the most difficult of any of those that survived. The acidosis factor appeared to be less pronounced than in some of the other cases but vomiting and impending cardiac failure were menacing features and only the tireless vigilance and courageous measures used by Dr. Hauser and Dr. Thompson of our staff saved the patient.

CASE XIII.—M. B., aged twenty-six years, was admitted to the hospital March 26, 1923. He had had diabetes about two years and had lost about 40 pounds. On the day before admission the patient had cramps in the abdomen, headache, and was short of breath. He was excessively thirsty but vomited whatever he drank.

At the time of admission the patient was drowsy. The temperature was 98° F., pulse 134, and respirations 42. Hypotension of the eyeball was noted and the reflexes seemed abolished. The appearance of the mouth and pharynx and the feeling of the muscles indicated severe desiccation. Iletin was given at once. The bowel was cleaned and instillations of glucose and soda started. After several attempts to give fluid by mouth, which induced vomiting, the stomach was lavaged and fluid by mouth discontinued. During the first twenty-four hours 900 cc of physiological saline was administered by hypodermoclysis. Small amounts of the saline were given intravenously and were injected into the peritoneal cavity. The pulse was small and rapid and at times cardiac failure was impending. For this caffein and digitalis were given hypodermically. After the patient has been under treatment about twenty hours there was a sudden collapse. It seemed at the moment that this might be due either to heart failure or to excessive iletin. Glucose was injected into a vein and cardiac stimulants used. The condition gradually improved but not promptly. The iletin dosage had been liberal; 30 units were given on admission at 6 A.M.; 20 units at 7 A.M.; 15 units at 8, 9 and 10 A.M.; and 10 units every two hours thereafter till midnight when the urine was free of glucose.

The blood taken shortly after the first dose of iletin contained 357 mg. per cent of sugar and the CO_2 was 15.7 volume per cent. Four hours later the sugar was 250 mg. per cent and the CO_2 24 volume per cent. After twenty hours the patient gradually improved and is now in excellent condition and taking a liberal diet.

CASE XIV.—D. G., aged thirty-one years, had discovered as a result of examination for insurance a year ago that he was diabetic. He had had no symptoms till about three months ago. Two days before I saw the patient he had taken cold and had fever; the following day he was drowsy and feverish, and during the night had some difficulty in breathing. In the morning of February 5 he was semi-conscious. When I saw the patient with Dr. Schultheis at noon he was stuporous but could be roused to answer questions. Air-hunger was notable and the intraocular tension was reduced. The urine contained about 6 per cent of sugar and gave strong reactions for ketones. Blood taken at this time contained 0.656 mg. per cent sugar and the CO_2 combining power was 14 volume per cent. The first dose of iletin, 20 units, was given about one o'clock and 10 units more at three o'clock. The usual supplementary measures were commenced. At three o'clock there seemed definite improvement; the patient was roused and discussed his treatment. About four o'clock the pulse become very rapid, 140, and later irregular and the patient seemed in collapse. Cardiac stimulants including adrenalin were given without notable result. During the next couple of hours the condition appeared more and more like that of cardiac failure. Dyspnea persisted but the respirations had lost the typical air-hunger character. Death occurred about six o'clock the same day.

The following case presented an unusual clinical picture. The signs in some respects were not those of diabetic coma, but the progress of the disease is most suggestive. It is unfortunate that adequate laboratory data are not available, the critical day of sickness having fallen on a Sunday.

CASE XV.—J. F., aged fifty-one years, a case of Dr. B. S. Barringer, had had diabetes about twelve years. By using moderate restriction of diet he had maintained good health and had not been restricted in his activities. Early in 1923, he developed symptoms which resulted in his consulting a genito-urinary surgeon. Cystopic examination revealed a malignant papilloma of the bladder which was treated with radium. Following this treatment there was retention of urine and an excessive irritability of the bladder necessitating frequent catheterizations—for a period, every two hours, day and night. It seemed desirable to give attention to the diabetes in order to reduce the urine volume primarily and also to improve the patient's condition sufficiently to permit completion of the urological treatment.

At this time the patient seemed to present a problem of no unusual difficulty. He was weak and emaciated but there was no evidence of significant infection. The temperature, pulse and respirations were normal. The urine volume averaged about 2 liters and contained 80 to 90 gm. of glucose; there was a moderate

acetone reaction, but none with ferric chloride. The blood sugar was 250 mg. per cent, which seemed at the time moderate in degree. Nephritis was suspected but no supporting evidence was secured; the urea nitrogen of the blood was 13.8 mg. per cent. The patient was given a diet containing 1800 calories and 75 gm. of carbohydrate and iletin treatment was started with a dose of 45 units per day. He was encouraged to drink as much water as possible.

The following day there had been no abatement of the glycosuria and since the iletin dosage seemed too large to continue with only a moderate elevation of blood sugar, it was given in 5-unit doses every two hours and each voiding of urine (catheterization) tested for sugar. Fifty units were given without detectable effect during the day. The patient seemed very weak and intoxicated but did not then impress me as suffering from acidosis. The morning of the third day he was definitely worse. He was rather drowsy, the respiratory rate had increased to 40 and the tongue was dry. The patient had no appetite and the diet was discontinued. He was given as much orange juice as he would take and a liter of milk. A solution of 5 per cent glucose and 3 per cent soda bicarbonate was injected by the Murphy drip method at intervals. During this day about 1800 cc of water was given intravenously and subcutaneously. Alkalies were administered in the intravenous solutions and by mouth. Twenty units of iletin were given at ten o'clock and the same dose intravenously at eleven; 10 unit doses were given every two hours till nine o'clock in the evening; a total of 110 units during the day. There was no abatement in the intensity of the glycosuria; ketone bodies were still present but the reaction with ferric chloride was faint. The patient was evidently becoming worse rapidly in spite of all that could be done. The pulse was weak and cardiac failure being feared, caffein was used intravenously. The same measures were continued till death occurred six hours later. The patient did not develop a typical coma. There was stupor but until an hour or two before death he could be roused. The respirations were at times 40 per minute but for some hours prior to death were 30 and were not characteristic though suggestive of acidosis. The temperature was normal. In the absence of necessary analyses of the blood I am uncertain whether this patient died of diabetic acidosis or some unrecognized complication. It is the only case I have seen in which iletin treatment produced no definite effect upon the glycosuria.

[We are glad to acknowledge indebtedness to the Eli Lilly Company for supplies of iletin (insulin Lilly) which were furnished gratis during the experimental period of its use.]

ILEOCECAL INCOMPETENCE. A CLINICAL ANALYSIS OF 1000 CASES WITH SOME DEDUCTIONS THEREFROM.*

By Noble Wiley Jones, M.D.,
PORTLAND, OREGON.

(From the Department of Medicine University of Oregon Medical School.)

Incompetence of the ileocecal valve as a cause of subjective symptoms has been a matter for controversial discussion for a number of years. The varying views have ranged from a dogmatic denial of all significance and the assumption that all persons have a variable degree of ileocecal regurgitation[1] to the other extreme that the finding of this condition in a medically irrelievable degree may be a fit indication for surgical interference.[2] Because of these varying views and also because of the general indifference to, and lack of present-day knowledge of, motor disturbances of the gastro-intestinal tract, we have recorded as carefully as possible all roentgenological abdominal data with the view of analyzing it in relation to this condition, when we had accumulated a sufficiently large number of cases to make such a study worth while.†

Regurgitation through the ileocecal valve has been known for a long time. Cannon, Keith, Elliott[3] and others have studied it experimentally. Cunningham[4] has described anatomical variations in the structure of the valve. Case[5] first found the condition roentgenologically in 1910, and this was verified and acknowledged soon afterward in Europe by Schwartz, Holzknecht and Singer[6] of Vienna and others.

It soon became the opinion of many different roentgenologists and clinicians[7] that incompetency of the valve was a very frequent condition and that the former of the two above mentioned views was incorrect. It has been, therefore, with the idea of attempting to see if some general conclusions might be formulated that this study was undertaken; whether local or general symptoms might

* The following clinical analysis of gastro-intestinal patients presenting a variable degree of ileocecal incompetence was made during the years 1914 to 1919, and the present paper was in most part written during that period. During the past four years these observations have been carefully weighed in the study of further material and the result of this added experience together with the longer observation of many of the older patients justifies us in presenting our conclusions as they were formed at that time. Naturally, but few miscellaneous reports on the subject appeared during the period of the war, although previous to it a number of controversial papers were written and an unjust amount of adverse criticism was expressed. Recently, Bryant of Boston, has again emphasized the necessity of placing some clinical significance upon the presence of ileal regurgitation in persons suffering with chronic gastro-intestinal symptoms, an effort that is wholly in accord with our experience.

† In a recent personal communication from Dr. Kellogg, he writes me that he has operated upon only 2 patients for ileocecal regurgitation without the coexistence of some distinct surgical lesion within the abdomen, and then only after the complete failure of medical control.

be referred to the presence of regurgitation; whether or not these symptoms could be removed by a medical or dietetic plan of bowel regulation; and also, if possible, to judge whether surgery should ever be entertained even in those cases in which symptomatic relief is not given by medical means and the patient distinctly suffers. The diagnosis of the so-called border-line abdominal diseases, into which problem motor disturbances of the gastro-intestinal tract enter so prominently, may never reach that degree of perfection where one may always say with positiveness, for instance, that a latent gall-bladder disease does or does not exist. To the surgical mind it may always be justifiable to explore the abdomen in an effort to find the cause of symptoms, but the trouble lies in the fact that many cases are explored surgically without relief to the patient or increased knowledge to the surgeon, who then dismisses the matter with the general diagnosis of neurasthenia. In the year 1915, roughly 70 per cent of our hospital patients suffering from gastro-intestinal symptoms had already been operated upon for supposed chronic appendicitis or some assumed pelvic disturbance without the relief of their symptoms. So many patients with such histories continue to be seen that it is quite justifiable to say that these mistaken diagnoses are being made quite generally today. The end-results of patients of this group treated medically after they had been operated upon for either actual or fancied surgical conditions within the abdomen justifies one in the belief that the symptoms were originally due to motor disturbances of the gastro-intestinal tract, often in association with a general asthenic state.

The clinical analysis of any large group of cases, without a determined pathological basis, especially when a number of years had elapsed during its accumulation, is open to evident criticism. This may be due to many things; changing interpretation of the same clinical findings, changing technic, the influence of advancement made in related fields, as, for instance, the bearing which the newly acquired knowledge of the physiology of the gastro-intestinal tract has upon this particular group of cases, etc. Personal bias may in a measure be eliminated by having different workers pass upon the interpretations. The roentgenological data of this group have been obtained in this manner. Where possible the cataloguing has been done by nurse assistants. In other words, an attempt has been made to rule out gross errors. One may say, furthermore, that the majority of the cases making up this group are instances of motor disturbances of the gastro-intestinal tract. It is not probable that a large percentage had unrecognized local lesions, such as gall-bladder and appendix affections or duodenal ulcer, for, in case of any doubt, these have been excluded. Neither should one assume that all of the symptoms experienced by these patients have been due to an ileocecal regurgitation. Rather have we

looked upon the incompetence as a factor, more or less marked in different cases in a general gastro-intestinal motor disturbance—more often a minor factor. Therefore, these cases in general represent a group of chronic gastro-intestinal patients, who, for the most part, have sought relief from gastro-intestinal symptoms. They have been tabulated for the reason that in the course of their examinations a variable amount of ileocecal regurgitation has been encountered, and local abdominal lesions, aside from pericolic bands, could reasonably be excluded.

TABLE I.—SEX AND AGE INCIDENCE IN 500 CASES OF ILEOCECAL INCOMPETENCE.

Degree of incompetence.	No. of cases.	Male.	Female.	Age.					
				1 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 and over.
+ and ++	359	143	216	10	87	126	70	55	19
+++	106	34	72	2	17	40	24	19	5
++++	35	8	27	..	5	17	4	8	1
Totals	500	185	315	12	109	183	98	82	25

In Tables I and II, the first 500 cases have been analyzed more in detail. In the course of this analysis there has been noted a strikingly large percentage of patients of the general asthenic type of build and with right colons loosely fixed in the abdomen, usually in conjunction with mobile cecums. For this reason a larger number, namely, 1000 cases have been analyzed to determine the incidence of mobile cecum to ileocecal regurgitation, and these figures are given separately in Table III.

The important point noted in Table I, if we can ascribe any causative relation between ilecocecal regurgitation and a loosely fixed right colon, is the preponderance of females having a regurgitation, namely, 315 to 185. Wolkow and Delitzin[8] in 1899, by means of sections and plaster-of-Paris casts, showed that the structure and configuration of the female pelvis was conducive to a ptosis especially of the right kidney and a lack of proper rotation and fixation of the right colon. Later this was varified by Coffey[9] by means of cast work.

The more detailed analysis of symptoms in Table II gives prominence to pain, gas, constipation and the so-called toxic symptoms. A twelve-hour ileum stasis occurred 204 times and 97 had undergone appendix or pelvic operations, roughly 20 per cent. According to the patient's histories, seemingly most of these operations were undertaken because of the presenee of abdominal distress. In regard to a possible underlying chemical cause for the so-called

TABLE II.—SYMPTOMS NOTED IN 500 CASES OF ILEOCECAL INCOMPETENCE.

Degree of incompetence	No. of cases.	Gas.	Pain.	Nausea.	Vomit.	Constip.	Dysen.	Alter.	Toxic symptoms.	Gen. asth.	Achylia.	Stasis.		Duo. drag.	Mucous colitis.	Epileptoid attacks.	Appendectomy.	Pelvic operations.
												Il.	Duo.					
+ and ++	359	227	196	59	41	256	20	9	274	161	17	159	63	18	12	2	47	16
+++	106	73	64	25	19	73	4	2	89	46	10	36	15	7	4	1	14	12
++++	35	29	21	8	6	28	1	..	26	12	2	9	5	2	3	..	3	5
Totals	500	329	281	92	66	357	25	11	389	219	29	204	83	27	19	3	64	33

toxic symptoms—dulness, languor, dull headache, despondency, etc.—as Mutch[10] believes there to be, we can add nothing except our clinical data. The opposing work of Mellanby[11] and others, and the deducted views of Alvarez[12] are not conclusive to us, for we have seen clinically examples of chronic diarrhea due entirely, it would seem, to an ileal stasis and regurgitation, accompanied by marked depression, languor, etc., disappear entirely by dietetic measures, with the relief of the stasis. Likewise, the chronic constipation case, No. 4254, detailed below, is difficult to understand except from the standpoint of a chemical poisoning. It is to be noted that, roughly, 70 per cent of the cases complained of these toxic symptoms.

TABLE III.—A REPORT OF 1000 CASES SHOWING RELATION OF MOBILE CECUM TO ILEOCECAL INCOMPETENCE.

Degree of incompetence.	Total.	Mobile cecum.	Fixed cecum.	Per cent. Mobile cecum.
+ and ++	695	556	139	80.0
+++	232	212	20	91.3
++++	73	65	8	89.0
	1000	833	167	83.3

Table III details the most striking and the most interesting feature of the group analysis; namely, the very high percentage of mobile cecum found in patients having ileocecal incompetence. The interpretation of mobile cecum roentgenologically is open to criticism for it must necessarily be an arbitrary one. Our associates, Drs. Palmer, Payne and Trahar, have arbitrarily designated a mobile cecum as one which can be moved vertically upward from $3\frac{1}{2}$ to 4 inches or more, as shown by comparative screen examinations in the upright position and colon enema examinations in the prone position. The cases also in which the cecum lies low in the pelvis and cannot for any reason be raised, and where there is an accompanying asthenic build with right kidney and stomach ptosis, have been likewise included in this group. The degree of mobile cecum, as also the degree of ileocecal incompetence, has been arbitrarily designated as 1+, 2+, 3+ and 4+. In extenuation of this way of determining a mobile cecum, we may say that very few patients in whom such findings have been made and who have come to abdominal operation for any reason, have failed to show a more or less movable cecum. The majority of these patients have also shown a right colon suspended by its own mesocolon, which in turn has not, in its development, become attached to the kidney shelf but hangs from a position near the mid-vertical line.

With 83.3 per cent of the 1000 cases showing a determinable degree of cecum mobility, one must believe that more than an accidental relationship exists between the two. In fact in the majority of the irrelievable cecum stasis cases which have come to operation the most important operative point in obtaining relief of symptoms has been the proper placement of the right colon on the kidney shelf. Some of these patients have not shown accessory bands, so that local pain and tenderness is not to be explained in them by traction upon such bands.* Again, and this is of the utmost importance, such individuals who have failed to respond to reconstructive methods and have remained weak and so-called neurasthenics, have found that their colons could be easily regulated, their bodies redeveloped and their asthenic and neurasthenic states overcome after the right colon had been so placed in the right paravertebral niche. These colons have appeared clinically as though the absence of this fixed point of purchase against which the musculature of the bowel may pull was the principal factor involved. That means that in these individuals it would appear clinically as though this factor was able to offset the peristaltic gradients, the influence of intra-abdominal pressure, the support of the anterior abdominal wall, the type of the bowel content, etc., combined. As will be seen below, this point has entered into a certain number of the cases placed in this group as having ileocecal incompetence.

The details of the findings in 20 ordinarily healthy persons who had no constipation, abdominal distress or toxic symptoms are given in Table IV. It so happens that out of 6 cases showing five, 2+ and one, 3+ ileocecal regurgitation, 5 of these had mobile cecums, or 83.3 per cent. Of the 10 cases of regurgitation of all degrees 6 had mobile cecums, or 60 per cent. These examinations were made in 1917. It is of greater interest to learn that one year later, following a light attack of influenza, Case No. 13, an asthenic built but very strong girl, who showed originally a mobile cecum, ileum stasis and a 3+ regurgitation, developed a marked general asthenia with constipation and attacks of pain and local tenderness in the right lower abdominal quadrant, which continued for

* Case: Discussing the relation of ring constriction waves in the cecum to cecal stasis, says: "When these ring constrictions . . . persistently fail to empty the tip of the cecum, it may be inferred that the cecum is fixed by adhesions, frequently associated with appendix disease. This finding suggests that it is the fixed rather than the freely movable cecum which is likely to give rise to stasis, and it would indicate that undue importance has been attached to the condition known as mobile cecum; that adhesions and fixation of the cecum are likely to give rise to evil consequences rather than mobility, and that harm rather than good may be done by operations for fixation of the cecum." It is true that the majority of cecum stasis cases are seen at operation to have associated pericolic bands, but we have the records of a number of cases of mobile cecum with irrelievable cecum stasis, constant tenderness and periodic attacks of pain in which no adhesions and no appendix disease were found at operation and which now show good postoperative end-results.

several months. These symptoms and the general asthenia were later overcome in a dietetic and reconstructive manner.

TABLE IV.—INCIDENCE OF ILEOCECAL INCOMPETENCE IN 20 HEALTHY PEOPLE.

		M.	F.	Age.	Type.	Mobile cecum.	Ileum stasis.	Regurgitation.
1	F.	..	+	33	Asth.	+++	O	+
2	R.	..	+	18	Sth	O	O	++
3	L.	..	+	18	Sth	+	O	++
4	J. a.	+	..	50	Sth	+	O	O
5	J. b.	..	+	14	Sth	O	+	O
6	J. c.	+	..	10	Sth	O	O	O
7	K.	..	+	28	Sth	+	O	O
8	C.	..	+	32	Asth.	+++	O	O
9	Fa	..	+	24	Asth.	++	O	++
10	T.	..	+	28	Asth.	++	+	++
11	H.	..	+	20	Sth	+	O	++
12	Mc	+	..	56	Sth	O	+	+
13	Mc 2	..	+	18	Asth.	+++	++	+++
14	B.	..	+	19	Sth	O	+++	+
15	Tr.	+	..	45	Sth	O	O	+
16	P.	+	..	32	Sth	O	O	O
17	J. 1	+	..	42	Sth	O	O	O
18	J. 2	..	+	36	Sth	O	O	O
19	J. 3	+	..	8	Sth	O	O	O
20	J. 4	+	..	5	Sth	O	O	O
	Totals	8	12			9	5	10

In 6 cases of 2+ and 3+ ileocecal incompetence 5 cases or 83.3 per cent showed mobile cecum.

Several roentgenologists have expressed informally the opinion that all normal ileocecal valves could be made incompetent if a barium enema were allowed to remain in the colon a sufficient length of time. To test these statements we have held 10 patients, who at their first examination had shown no ileocecal regurgitation, under observation for one hour, with the results shown in Table V. These results indicate that the ileocecal valve may at times be fully competent for the duration of one hour, even in the presence of a mobile cecum and distinct motor disturbance of the gastrointestinal tract. The first and second examinations were always made on different days.

Illustrative Case Records. In the study of the cases, varying conditions and varying responses to treatment have been met. One may easily separate them into groups according to their response to treatment and the methods of treatment employed. Behind them all, it would seem to us, lies the fundamental principle of maintaining a regulated gradient of intestinal forces, as will be mentioned later. There were patients who received symptomatic

relief from dietetic and physical reconstruction methods, both with the removal of the ileocecal regurgitation and without its removal. There were others who were treated surgically, both with and without relief; and also 1 case of partial colectomy and 1 case of Lane's short-circuit operation have been appended because each showed the greatest possible degree of ileal stasis and regurgitation with symptomatic relief from medical measures, although such cases have not been included in the list of 1000.

TABLE V.—ILEOCECAL COMPETENCY AS SHOWN BY 10 PATIENTS UNDER OBSERVATION FOR ONE HOUR.

Case No.	Diagnosis.	1st examination.	2d examination. Minutes.				
			0	15′	30′	45′	60′
A 14964	Chr. gall-bladder; periduodenal bands, colon stasis, mobile cecum +	O	tr.	−	+	−	tr.
A 18538	Gen. asthenia, colon stasis, mobile cecum 2 +	O	O	O	O	O	O
A 18746	Gen. asthenia and ptotic mobile cecum +	O	+	−	−	tr.	++
A 18615	Gen. asthenia and ptotic, cecal and colon stasis, mobile cecum 3 +	O	O	O	O	O	O
A 18774	Chr. gall-bladder; ileum and colon stasis, mobile cecum +	O	O	tr.	O	O	O
A 19374	Dental sepsis, gastro-intestinal sequelæ, mobile cecum O	O	O	tr.	O	O	O
			0′	20′	40′		60′
B 258	Sinus infection, chr. appendicitis and local peritonitis, mobile cecum O	O	tr.	O	−		tr.
B 566	Gen. asthenia and ptotic, colon stasis, mobile cecum +	O	O	O	tr.		−
B 595	Ext. gen. asth., colon stasis, mobile cecum 2 +	O	O	O	O		O
B 73	Post influenzal gen. asth., ptotic, colon stasis, mobile cecum 3 +	O	O	O	O		O

The cases have been grouped, therefore, in the following manner, and under each heading a few briefly detailed illustrative case records are given to emphasize the points in question.

GROUP I. Those cases which responded to medical treatment with satisfactory symptomatic relief.

GROUP II. Those cases which failed to respond to medical treatment and did not come to operation.

GROUP III. Surgically treated cases into the symptom complex of which entered the question of ileocecal regurgitation.

(*a*) Medically irrelievable cases associated with mobile cecum.

(*b*) Medically irrelievable, uncomplicated ileocecal regurgitation.

And also:

(*c*) Partial colectomy, without relief of symptoms.

(*d*) Lane short circuit operation, without relief of symptoms.

GROUP I. *Those cases which responded to medical treatment with satisfactory symptomatic relief.*

Medical Case No. 6327, November 17, 1915. A woman, aged twenty-four years, married, nullipara; of moderate asthenic type of build with movable cecum, was always in good health until the beginning of her present illness. In June, 1914, the patient suffered an acute attack of appendicitis with rupture. Appendectomy was performed and the patient recovered from the effects of the acute illness and operation. In September of the same year there began nausea, stomach distress, and vomiting usually taking place in the evening following dinner. The bowel remained regular except for slight periods of looseness and considerable gas and bloating that was relieved by the passing of flatus. Physical examination of the patient was negative throughout with the exception of a tender, spastic cecum and colon. A 4+ ileocecal regurgitation was present. Response to the principles of bowel regulation was prompt with complete relief of symptoms, which condition has remained to date, seven years later. This patient had been frequently urged to submit to further surgery for the relief of adhesions.

Medical Case No. 13184, May, 1919. A female, aged thirty-four years, para I, of moderate, squatty type of build with slight postural scoliosis was in good health until the beginning of her present trouble eight years ago. The patient then became distressed with an irregularly recurring drawing pain in the stomach which was relieved by lying down, the applying of heat, or by eating. Following the taking of food the pain would again recur in two hours. There was no belching, nausea or vomiting. At the same time pain occurred in the right side of the abdomen, of a dull nature, with local soreness but never accompanied by fever, nausea or vomiting. During the period of the distress the patient could not lie on the right side because of this pain. The bowel had moved regularly for the most part with occasional periods of slight looseness with shreds of mucus. General physical examination revealed normal findings with the exception of a 4+ ileo-

cecal regurgitation and a 1+ twelve-hour ileum stasis. The patient responded quickly to the principles of bowel regulation and obtained definite relief of all symptoms together with nearly a complete removal of the ileocecal regurgitation. This patient has had the diagnosis of chronic appendicitis made repeatedly and advised to be operated upon for it.

Medical Case No. 6292, February, 1916, a male, aged forty-six years, of heavy, squatty type of build, was always of robust health. For the past twenty-five years the patient has had irregular periods of dizziness, fever, sweating and chilliness associated with gas, belching and looseness of the bowel; the so-called toxic symptoms being very marked and always accompanied with much nervousness and psychical depression; never did he suffer pain, nor was the bowel ever constipated. General physical examination between these periods of distress revealed normal findings throughout. During the period of attacks ileocecal regurgitation alone was determined. These attacks seemingly recurred whenever the patient left his routine habits of living. Frequently they would appear while he was in camp on fishing or hunting trips, and during a period of three years he would place himself under rigid dietetic control for a short time in order to overcome these symptoms. At no time was there any suggestion of other pathology found in the numerous examinations made upon him. It was often believed that a hidden gall-bladder disease existed to explain his recurring attacks. In January, 1919, the patient died with the picture of an acute infection characterized by an onset similar to the above mentioned attacks, which rapidly passed into a state accompanied by increasing urinary suppression, a toxic jaundice, increasing pulmonary edema, and on the day preceding death, auricular fibrillation. Autopsy performed a few hours after death revealed a small area of bronchopneumonia at the base of the right lung with gray hepatization, but no other strictly local lesions. The gall-bladder and appendix were normal. The ileocecal valve appeared entirely normal in its anatomical structure. Death probably was due to an acute influenzal infection which was masked by symptoms first referred to the kidney and liver. No further explanation for the occurrence of the patient's periodic attacks during life was obtained, so we were forced back to the assumption that his recurring illnesses were in some way associated with his periodic ileocecal regurgitation.

Medical Case No. 3598, June, 1916. A male, aged forty-eight years, heavy, squatty type of build, was always in robust health until the beginning of the present trouble. Four years ago the patient began to have irregular bowel movements with tendency to diarrhea. Frequently a loose stool was passed immediately

after eating, and occasionally constipation existed. About eight weeks ago the patient was seized with severe pain in the lower right abdominal quadrant, without fever but with nausea and vomiting. No local soreness existed. The attack lasted two or three days. A second similar attack occurred three days preceding date of examination. There was a sharp, colicky pain in the region of the appendix, which was promptly relieved by using a warm water flushing. There was but little soreness or gas. General toxic symptoms consisting of dulness, languor, dull headaches together with mild muscle and joint pains had existed throughout the preceding four years. At this time our physical examination revealed normal findings with the exception of dental sepsis and a marked ileocecal regurgitation. Under the principles of dietetic bowel regulation and the removal of several abscessed teeth, the symptoms promptly cleared. Most striking was the relief of the feeling of languor and depression, the patient's head became more clear and he went about his work, that of a travelling salesman, with much more spirit and ambition. A few months later, while in the Middle East, he suffered a third attack of pain in the right lower abdominal quadrant, at which time a calculus was located in the right ureter and removed by operation. Following the operation the patient's former looseness of the bowel returned together with the old symptoms of mental depression, dull headaches, with his former lack of power of concentration. This continued until he again consulted us in March, 1918, at which time a marked degree of ileocecal regurgitation was again found. Again he responded to dietetic bowel regulation with the relief of the symptoms, and at the time of the last report, one year ago, the patient was feeling entirely well by following this regimen.

GROUP II. *Those cases which fail to respond to medical treatment and did not come to operation.*

Medical Case No. 6916, February, 1917. A female, aged thirty-four years, para II, heavy, squatty type of build, she had always been physically strong and well with the exception of severe headaches which began in childhood. Fourteen years ago there began constipation, a cathartic habit, gas, bloating, belching, colic pains throughout the bowel, much soreness along the line of the colon together with continued headaches and marked toxic symptoms. The patient felt dull, stupid, dizzy, sleepy, with cold hands and feet, and was excessively nervous. These symptoms have continued irregularly but constantly for the past fourteen years. Physical examination revealed normal findings with the exception of a tender, spastic colon. Moderate duodenal lagging and very marked ileocecal regurgitation were noted. The cecum and ascending colon appeared normally fixed upon the kidney shelf. For a

period of three weeks this patient was under control in the hospital without relief of her symptoms and without obtaining a dietetic regulation of the bowel. Abdominal exploration was not accepted, and the patient continued at last account with the same degree of symptoms. Without more exact information it has been assumed that this patient is suffering with an irrelievable type of ileocecal incompetency.

GROUP III. *The remaining case histories illustrate different types of surgically treated cases, into the symptom complex of which entered the question of ileocecal regurgitation.*

A. Medically Irrelievable Cases Associated with Mobile Cecum.—Medical Case No. 7394, April, 1917. A female, aged twenty years, single, of a general asthenic type of build, was in moderately good health until three years ago. At that time she became run-down, lost weight and strength, and especially for the past year and a half has suffered much physical and psychical depression and bodily weakness. Since the preceding November she has suffered from severe shooting pains in the stomach, appearing immediately after eating, these passing straight through to the back and under the left shoulder blade. Nausea and vomiting following breakfast have occurred nearly every day since the onset, but is relieved during the latter part of the day, when the patient is able to retain most of her meal. Much burning in the stomach is experienced at night. There has never been constipation, but during the past year and a half she frequently has had periods of looseness of the bowel with gas and griping pain. She has also suffered constant aching and a dragging sensation in the small of the back while standing or walking, and frequently recurring headaches. The general physical examination was that of a tall, generally undernourished, asthenically built girl, a straight back type with a moderate postural scoliosis. The roentgen-ray examination of the abdomen showed a midline gastroptosis, freely movable cecum and ascending colon, duodenal drag with lagging in the second portion, and a filling defect in the bulbus, seemingly due to periduodenal bands; duodenal tenderness and a marked degree of ileocecal regurgitation. No relief was obtained in hospital by medical treatment during a period of three weeks. The operation revealed no further pathology. One acquired band extended from the duodenum to the transverse colon; a second band attached the colon to the parietal peritoneum. The operation consisted of appendectomy, plication of the cecum and the fixation of the right colon on the kidney shelf. After a period of four weeks the patient was returned to the Medical Hospital, where the general process of reconstructing the extreme general asthenic type of body build was instituted with the result that the patient has obtained a good degree of health and strength.

Medical Case No. 7268, April, 1917. A female, aged forty-one years, para I, of moderately squatty type of build, was in good health until seventeen years of age when there began symptoms of what was diagnosed as chronic appendicitis. Five years ago an appendectomy was done since which time the patient has never been well. At the time of her first illness there began cramping pains along the course of the colon, periodic nausea and vomiting, constipation with alternating dysentery, much mucus in clumps and strings in the stools, abdominal soreness, rheumatic muscle pains, and extreme nervousness. This has occurred in varying degree up to the present time. Physical examination revealed in the main normal findings; the colon was spastic and tender; the stools contained much mucus. Roentgen-ray examination of the abdomen showed marked duodenal stasis, 2+ twelve-hour ileum stasis, a marked degree of ileocecal regurgitation, mobile cecum, and a generally spastic colon. Effort in hospital, under control, to relieve the symptoms and regulate the bowel proved futile, and she was operated upon with the following operative findings: Cyst on the right ovary the size of a hen's egg, incompetent ileocecal valve, large dilated and flabby cecum which was entirely mobile, long mesentery which permitted the entire right colon and hepatic flexure being turned well out through the wound. The operation consisted of enucleation of the cystic portion of the ovary, repair of the ileocecal valve (modified Kellogg operation), plication of the cecum, and the fixation of the right colon. The patient believing that the surgical operation should relieve her of her symptoms, refused to submit to dietetic measures following it and went home without relief. A couple of months later her distress remaining as severe as before her operation, she submitted to dietetic control and was relieved in large measure of her abdominal pain and distress; the stools became regular and quite free from mucus. Later, believing herself quite well, she ignored her dietetic regimen with the result that she was soon back to the condition in which she had been for so many years. A little persuasion, however, induced her to return to a mechanically fine, bland diet, which she has since followed with definite satisfaction.

B. Medically Irrelievable, Uncomplicated Ileocecal Incompetence Cases.—Medical Case No. 4254, July, 1914. A male, aged thirty-two years, of gaunt, asthenic type of build. At the age of seven the patient began to have what was termed bilious attacks; a dull, occipital pain extending over the head back of the eyes, coming on at irregular times of the day and recurring at weekly to monthly intervals. In 1903, he became very nervous, irritable, irrational and suffered much from insomnia. He complained of the so-called toxic symptoms very markedly, with entire lack of concentration and ability to work. He was considered for some years mentally

unbalanced by his neighbors and the members of his own family. When first seen, in 1914, his physical examination revealed septic tonsils and a moderate degree of pyorrhea, a sallow, pigmented skin, a general abdominal ptosis of moderate degree, and normal stomach, blood and urine chemistry. Roentgen-ray examination revealed normal findings with the exception of a 4+ ileocecal regurgitation. The cecum and ascending colon seemingly were normally fixed upon the kidney shelf. For a period of one and a half years this patient was under more or less constant medical control both in and out of hospital. His septic tonsils and dental sepsis were removed; a moderate grade of ethmoid sinusitis treated, and an attempt was made to overcome his general so-called toxic symptoms by means of bowel regulation and the principles of body reconstruction, but only a moderate degree of success was obtained. At no time was the patient relieved of his feeling of mental depression, his headaches, his lack of interest and ambition. In May, 1915, an exploratory abdominal operation was performed and nothing but an ileocecal valve incompetence determined. Pericolic bands were removed and the Kellogg operation for incompetent ileocecal valve was performed. The day following operation, while visiting the patient, he described his condition as though a load had been lifted from his head. He stated that not for years had his head felt so clear and free from headache as it did that morning. He made a rapid convalescence and returned home feeling better than he had for years. He picked up in weight and strength rapidly and went to work on the farm. He felt very well for about nine months, when he returned with the statement that two or three weeks before he had begun to experience the same feeling of depression and head symptoms which he had had previous to his operation. Barium enemas again showed the presence of marked ileocecal regurgitation. He again asked to have the operation of closing the ileocecal valve repeated, but not believing it to be justifiable at the time, the patient was again placed upon the principles of rigid bowel regulation, forced feeding and physical gymnastics. During the succeeding years repeated barium enemas have been given, with the result that a marked degree of ileocecal regurgitation has always been found. On June 23, 1919, the following note was recorded on his history: "Patient's head has felt clear for the past two years; periodically, possibly once a week, he feels a hurting and tenderness about the region of the cecum—a feeling of blocking, although the bowel moves well each day. His general health has been improved; has continued his work on the farm without interruption." On this day a 4+ ileocecal regurgitation was again found by roentgen ray.

Medical Case No. 5175, February, 1916. A business man, aged thirty-three years, of gaunt, asthenic type of build, whose

general health was good until 1895, when distress began in the stomach, one to two hours after eating, associated with gas and an obstinate constipation. A cathartic and enema habit soon followed. The patient became nervous, apprehensive, lost in weight and strength and developed headaches. The general physical examination revealed normal findings. Roentgen-ray examination of the abdomen showed only a marked ileocecal regurgitation. In hospital, under control, it was found impossible to regulate the bowel or to relieve the patient's symptoms. In July, 1916, the abdomen was explored with the preoperative diagnosis of incompetent ileocecal valve and a possible gall-bladder infection because of suspicious shadows in gall-bladder films. The operative findings were adhesions folding the appendix on itself and attaching it to the parietal peritoneum; incompetent ileocecal valve; ascending colon normally fused; gall-bladder, stomach and other abdominal organs normal. The operation consisted of removing the appendix and repairing the ileocecal valve by the Kellogg method. Immediately following the operation very decided relief of the patient's head symptoms, together with the easy regulation of his bowel, was obtained. Later he had a return of his symptoms, but he has always been able to offset them by dietetic means, and his general health is much improved. We have never been able to reëxamine his intestinal tract by the roentgen ray since the return of his distress, but it is our belief that he has an ileocecal incompetency and that he is obtaining symptomatic relief by his bowel regulation.

C. Partial Colectomy Without Relief of Symptoms.—Medical Case No. 6511, December, 1916. A female, aged thirty-five years, para I, of general asthenic type of build, was never strong and always constipated from childhood. The patient's history is that of a severe general asthenic and ptotic individual with obstinate constipation with its usual train of accompanying symptoms. In February, 1916, a partial colectomy was performed for relief of her obstinate constipation in the Middle East by the Bloodgood method. Following the operation she had relief for about six months. Then the symptoms returned together with much pain, colic, gas and periodic loose stools. She rapidly lost in weight and strength again and her general health has been poor. An examination revealed a very asthenic, moderately straight back type of body build, pigmented skin, thin, emaciated abdominal wall with active peristalsis in the coils of the bowel visible through it. The new anastomosis of the ileum to the transverse colon together with a marked midline ptosis of the stomach, a twelve-hour stomach stasis, a duodenal drag, and a widely dilated terminal ileum with constant stasis was shown roentgenologically. Under control in hospital, it was found that the loose bowel movements could be overcome, the pain and sore-

ness and gas were relieved by dietetic measures, and the patient made very good progress toward rebuilding her general asthenic state. After six weeks in the hospital she returned home and continued to be well until the following fall, when the work and worry incident to taking care of a sick child again upset her bowel and was followed by a rapid loss of weight and strength and recurrence of her former symptoms. She returned to the hospital, was again reregulated and sent back home in very good health. For the third time she returned in the spring of 1919 with a moderate recurrence of her former symptoms. At this time a more complete carrying out of the reconstruction principles incident to her bowel regulation and her general asthenic type of build was done, and the patient returned home believing that she would then be able to maintain permanently a good degree of body health. At all times has there been present, both during her periods of physical weakness and bowel irregularity and during her periods of comparative good health, a marked degree of ileal regurgitation and dilatation.

D. Lane Short-circuit Operation, with Persistent Symptoms.—Medical Case No. 7439, May, 1917. A female aged forty-three, years, para II, of moderately asthenic type of build, had fairly good health in childhood and until eleven years ago when she was operated upon for a tuberculous peritonitis. Following this operation she became quite well, but six years ago a Lane short-circuit operation was done because of an obstruction of the bowel, as related by the patient herself. Following this operation she was again fairly well until two years ago when there began periods of pain, gas, bloating and vomiting, with acute attacks of severe looseness of the bowel, lasting about twelve hours each. With these recurring attacks the patient lost rapidly in weight and strength. This condition has continued until the present time. General examinations have shown in the main normal findings. Roentgen-ray examination of the gastro-intestinal tract showed clearly the ileosigmoidostomy and the large dilated ileum with its persistent stasis. The entire colon would fill with barium to the cecum where it would remain lodged for days. It was found on attempting to regulate the bowel that it was possible to overcome the gas and pain and periodic dysentery, to the end that the stools became regular and formed. The patient put on weight, gained in strength quite rapidly, and after six weeks in the hospital returned home very much improved in health. A year later she returned with a recurrence of the former symptoms. These were again quickly set aside and she returned home to continue for all times a rigid dietetic bowel control. Repeated examinations, both during the time of her illness and afterward, showed the same permanently dilated ileum with its persistent stasis. In spite of this condition the patient remains very well and strong.

Since the compilation of the above records was finished in 1919, 2 more patients suffering with an irrelievable ileocecal regurgitation and cecal stasis with mobile cecum have come to operation. In these 2 cases only the fixation of the right colon and cecum was done and no repair of the ileocecal valve was made because our experience with the previous ones had made us believe that in the cases in which there was a definite right-sided colon ptosis the important principle in the surgical treatment was the fixation upon the kidney shelf of the loosely attached bowel. Leaving the valve unrepaired in any way and noting the medical result after the operation would give one added evidence as to the correctness of the opinion that it was the influence of the added mechanical support of the fixation which actually permitted the cecum to empty itself, and gave to the patient relief from his symptoms. Both of these patients worked out in this way.

Medical Case No. 10897. A female, single, aged nineteen years, was first seen in 1918. The patient was of an extreme asthenic type of build, and never had been strong; she had suffered from constipation and so-called bilious spells more or less all her life. For the past three years she has suffered more from increasing weakness, nervousness, irregular pains after eating, colic distress through the bowel and frequent throbbing, dizzy frontal headaches with much nausea but no vomiting. Her examination showed an extremely asthenic, sway-back type of body build with marked postural scoliosis, a general abdominal ptosis, a dilated cecum lying low in the pelvis with a 3+ ileocecal regurgitation, but otherwise normal findings. For three weeks the patient was under control in hospital without relief from the cecal stasis or abdominal distress. Abdominal exploration was advised and was refused. In April, 1919, she was operated upon elsewhere for chronic appendicitis without relief of symptoms and with an increasing amount general body weakness and functional nervousness. In November, 1920, she returned to us and was again tested out in hospital with the same results as before. The patient had lost much in weight and strength and had become a profound neurasthenic. In spite of this condition we advised surgical relief and this was done November 22d. A marked right colon ptosis with a large dilated mobile cecum lying free in the pelvis was all that was found. There were no pericolic bands present about the bowel. A right colon fixation operation was done together with a plication of the cecum. The patient's convalescence was prolonged and very stormy because of an accompanying psychic imbalance which set in soon after operation and from which the patient has not yet fully recovered. The effect upon the bowel function, however, was very prompt. Complete regulation of the bowel was easily obtained, and the patient added weight easily, although strength more slowly. She

was last examined in January, 1922, and the bowel was found to be functioning normally. The presence or absence of ileocecal regurgitation was not determined. Her physical health is very good; psychically she is still upset although she is slowly working out this problem satisfactorily.

Medical Case No. 17954. A female, single, aged eighteen years, was first studied in December, 1920. The patient complained of much gas, bloating and colicky pains through the bowel. At times persistent diarrhea would occur together with nausea and uncontrollable vomiting, shortness of breath and pains about the heart accompanying the bloating. Toxic symptoms of dulness, weakness and nervousness were marked. Examination revealed a short, squatty built young woman with normal physical findings with the exception of a low-lying, freely movable cecum, a very spastic, tender colon and a 4+ ileocecal regurgitation. The patient was then placed in hospital under control and an attempt made to overcome the local stasis, but during a period of three weeks this was found to be wholly impossible. The vomiting and looseness of the bowel was much aggravated by the dietetic regimen. Later, at home for five months, the patient tried in vain to obtain relief by following the same principles more slowly. In May, 1921, the abdomen was explored with the belief that an unrecognized gall-bladder disease would be found. This, however, was not the case. The cecum and right colon were long and loosely attached. It could be entirely delivered outside of the abdomen. There were some bands about the colon, which extended to a point above the duodenum, and the appendix was long and free. The appendix and the pericolic bands were removed and the right colon fixed upon the kidney shelf. Recovery was prompt. The tender, spastic colon relaxed under a bland diet and the symptoms of vomiting and diarrhea disappeared rather quickly. The colon was examined by barium enema July 27, 1921, when a 3+ ileocecal regurgitation was still present; all diarrhea, however, had left. February, 22, 1922, the patient reported feeling perfectly well, and on that day a 1+ regurgitation was found.

Discussion. We have shown in our clinical work with gastrointestinal patients that the relief of symptoms does not depend upon the removal of an ileocecal regurgitation, and, also that a distinct ileum stasis is sometimes not recognized by ill feelings. We have likewise shown that some of these individuals have not obtained relief under the most careful control until after the loosely fixed right colon has been properly placed upon the kidney shelf, which alone seems to permit a regulation of the bowel that affords relief. The fixation of the colon alone seldom or never permits the bowel to regulate itself. A process of dietetic training, incident to the

tender, spastic colon, is necessary and oftentimes it must be carried out for a period of years. Again, other individuals with mutilated colons, short-circuitings, partial colectomies, colectomies, with a persistently dilated terminal ileum, persistent stasis and free regurgitation, may be made well and free of symptoms by proper control. Why are these things so? What fundamental principles of the gastro-intestinal tract underlie the relief from such varying pathological states? It is evident that if there is a common basis for these conditions it must be found in the motor mechanism of the bowel itself.

For some years the nodal and bundle system of the heart have been quite accurately known; the rhythmicity of the heart beat being directly under the control of these systems. In the 1915 Cavendish Lecture, Arthur Keith described certain more or less ill-defined nodal zones of neuro-muscular tissue in the intestinal tract—a supposed specialization of the myenteric plexus. He found these specialized zones about the cardiac orifice, the duodenum, the jejunal junction, the ileocecal region and in different portions of the colon and rectum. To them he ascribed a pacemaker function similar to those of the nodal system in the heart.

Recent advance in the knowledge of the motor function of the gastro-intestinal tract from the physiological side has become of greater importance and is much more satisfying in its conception of what actually underlies the mechanism of peristalsis. Much of the experimental work, as well as the conception of what these experiments have meant, has been done by Alvarez[13] of the Hooper Foundation of the University of California. To us his work gives an explanation of peristalsis that meets every clinical requirement, with the possible exception of a mechanical part played by a loosely attached cecum.

Gradients of rhythmicity, irritability, and of the latent period of contraction have been demonstrated in the stomach, small intestine, cecum and colon. Using the CO_2 production and the catalase content of the tissues (catalase is the ferment which liberates oxygen from hydrogen peroxide) as indices of metabolic activity, Alvarez has shown that similar gradients of metabolism exist more or less uniformly in a decreasing degree as one goes down the tract, and it is believed that it is this gradient of metabolic activity which gives rise to the gradients of rhythmicity, irritability and latent period that determine the direction of peristalsis.

Referring again to the heart, Hyman[15] has likewise found a gradient of metabolic activity underlying the difference in rhythmicity of the muscle bundle system of His.

Lower gradients of metabolic activity are found in the cecum than those which exist both in the terminal ileum and in the ascending colon immediately above the cecum. Excised muscle strips

from the cecums of rabbits and guinea-pigs show little tendency to contract rhythmically. The irritability is low and the latent periods are long. The catalase content of the tissues is low, indicating a low metabolic activity. There is, however, a gradient of catalase content from the tip of the cecum to the base, indicating a metabolic gradient which determines the direction of contraction waves when they occur. This motor mechanism of the cecum doubtless plays its role in the puddling of its contents, as it has been termed, and also aids in the absorption of its liquids. Is it then not logical to believe that a freely suspended, unattached cecum in man, who habitually assumes an erect posture, may lose enough of that mechanical support given to the firmly fixed cecum lying on the kidney shelf, a plane of about 50 degrees with the horizontal, to interfere with the emptying of its contents very much or even to make it impossible? This is exactly the condition met with clinically in some instances of mobile cecum, both with and without the presence of ileocecal regurgitation. This finding we have proven in a number of cases by demonstrating the irrelievability of the cecal stasis with the patient under rigid control, and then by noting its easy relief after a simple fixation of the cecum and ascending colon on the kidney shelf has been done. Clinically, the following general statements hold true; namely, abnormal cecal stasis is relatively seldom found in a firmly fixed right colon with a high position of the cecum; conversely, cecal stasis is frequently met with in a loosely suspended right colon with mobile cecum. The same statements are true of ileocecal regurgitation and of chronic constipation in general.

Another thing of great importance determined by Alvarez has been the fact that these normal gradients of rhythmicity, irritability, latent period and catalase content are much disturbed and disarranged by general illness, local abdominal lesions and by purgation. Muscle segments from the intestinal tracts of sickly animals, or from those that have been purged freely, beat poorly, irregularly, and become fatigued easily. We have known for years in a clinical way that the overcoming of a general asthenic state was one of the most important factors in overcoming the motor disturbances of the gastro-intestinal canal. In the same manner we have repeatedly shown the harmful effect of all catharsis in the regulation of chronic constipation. It is impossible to overcome an intestinal or colonic stasis and make use of catharsis at the same time, or even of flushings and enemas to any extent. This principle is fundamental. An intestinal stasis which can not be overcome by dietetic methods under rigid control has some form of surgical barrier present in the abdomen which prevents it. It may be a hidden gall-bladder or appendix disease; more rarely is it ulcer or widespread pericolic bands; and still more rarely is it an irrelievable intestinal stasis itself. This principle forms the

basis of what we choose to call our "therapeutic test" of the so-called borderline abdominal case. A patient with chronic abdominal symptoms, in whom no satisfactory explanation for the symptoms can be found by examination, is put through this therapeutic test before operation is advised. Many hidden surgical lesions are found in this way because such lesions will often produce an acute upset under the pressure of a bowel regulation regimen. On the other hand, a much greater percentage of patients with similar symptoms are relieved quickly of distress and the basis of it is shown to be some form of a relievable motor disturbance by its quick response to the same procedure. Ileocecal regurgitation, with and without other local lesions, occasionally, although rarely, enters the field of true surgical indications. It is by this therapeutic test that we have separated the few surgical from the many dietetically controllable cases.

Conclusions. 1. Competency of the ileocecal valve in some persons may be demonstrable throughout a period of one hour. It may be assumed to be permanent in them.

2. Ileocecal incompetency occurs without symptoms in a moderate percentage of healthy persons. The majority of the instances occur in conjunction with a mobile cecum. In such persons the degree of regurgitation is usually small.

3. The incompetency is of frequent occurrence in persons who have abdominal distress.

(*a*) The relief of such symptoms may or may not be accompanied with the overcoming of the regurgitation.

(*b*) The relief of such symptoms seems to be directly related to the reëstablishment of the normal gradient of intestinal forces, as suggested by Alvarez's work.

4. Over 80 per cent of cases of ileocecal incompetency occur in association with a determinable degree of cecum mobility.

5. A small number of ileocecal regurgitation cases, with and without mobile cecum, are found in which neither the stasis nor the symptoms of it can be removed by dietetic measures alone. The end-results following the surgical treatment of such cases justify the surgical measures employed.

6. The operative procedures alone do not relieve the patient of his distress. They merely place the patient back into the large group of relievable cases which depend upon dietetic and reconstructive methods of treatment for their cure.

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EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS, AS DEDUCED FROM A MILD EPIDEMIC OCCURRING IN THE 8TH CORPS AREA, MARCH, 1922.

By Lewis B. Bibb, M.D.,
CAPTAIN, M.C., U. S. A., CARLISLE BARRACKS, PA.

About March 1, 1922 a sudden outbreak of acute respiratory diseases occurred among troops stationed near San Antonio, Texas. The brief duration of the epidemic, its rapid development and equally rapid decline, challenged investigation and eventually led to a comparison with other local epidemics occurring in different stations of the 8th Corps Area (shown in Fig. 4).

The persons affected were for the most part not dangerously ill. There were no deaths among 650 cases admitted to Station Hospital, Fort Sam Houston, Texas. Temperatures averaged 102° F. among the different cases, although individuals occasionally showed fever up to 104° F. The symptoms were those usually described in mild or moderately severe catarrhal fever. Onset was usually with generalized aching, headache, prostration, chilly sensations giving way to fever, cough and often some soreness of the throat. Most of the patients felt well after two or three days in the hospital and were able to return to duty within a week or ten days. There was no pneumonia or empyema, except perhaps in one or two instances. Sinusitis occurred only rarely.

In view of the lack of definite diagnostic points for identifying influenza, it was deemed advisable to follow the plan advocated by the Surgeon-General in the following words which he applied to the epidemic of 1918: "The only way to obtain a correct picture of the epidemic during the autumn (1918) is to combine both the admissions and the death rates of pneumonias, of influenza and of the common types of respiratory diseases. The excess then of the combined rates over the ordinary rates for this class of diseases for the same period of the year will probably give approximately the correct figures for influenza with its complications."

The accompanying charts and graphs represent therefore all cases of pneumonia, influenza, and ordinary types of respiratory

diseases occurring within certain organizations and certain stations during the first three months of 1922. Fig. 1 represents the epidemic as it was reflected in the daily admissions to Station Hospital, Fort Sam Houston, Texas. The number of admissions for acute respiratory disease increased rapidly from an average of 1 or 2 cases daily up to 46 cases on March 10. The decline in numbers was almost as rapid, having reached an average of 3 or 4 cases daily by April 1. On Saturdays and Sundays there were fewer admissions, due to the reluctance of soldiers to report sick on holidays. A miniature preliminary epidemic or "flare-up"

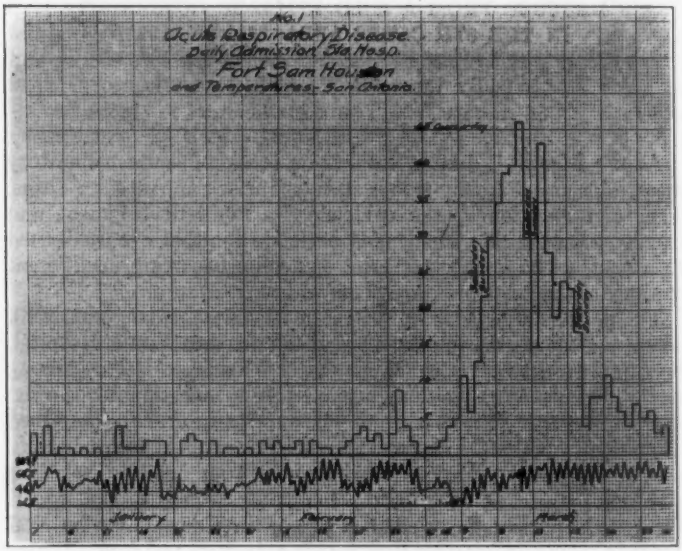

FIG. 1.—Showing number of admissions daily due to acute respiratory disease; Station Hospital, Fort Sam Houston, Texas, first quarter of 1922. Also showing fluctuations of temperature at United States Weather Bureau observation station two miles away.

occurred on February 21. This miniature forerunner of the large epidemic, had it affected only one station or organization, might have been plausibly regarded as the focus from which the larger epidemic developed. As a matter of fact, however, the group of 9 cases came from the following sources: Infantry A, Camp Travis, 2 cases; Infantry D, Camp Travis, 1 case; Camp Stanley, 2 cases; Camp Normoyle, 2 cases; Fort Sam Houston, 1 case; Station Hospital (attendant) 1 case. When analyzed, therefore, this group partakes more of the nature of a group of sporadic cases. During January and February, sporadic cases occurred in a more

or less irregular series from the various organizations, as shown in Figs. 2 and 3. Unquestionably, there was a "flare-up" about February 15 to February 22, especially shown in Fig. 1.

Fig. 3, however, shows all cases that appear in Fig. 1, and also those cases at certain nearby stations that were not sick enough to be transferred to Fort Sam Houston. Fig. 3 therefore, shows that Camp Stanley, twenty-three miles north of Camp Travis, and Camp Normoyle, four miles west of Camp Travis, were affected by a milder and earlier epidemic than Camp Travis. There was abundant passing back and forth between Camp Stanley and Camp Travis. Regiments of engineers, of infantry, and of artillery marched to Camp Bullis adjoining Camp Stanley, camped there for days and marched back to Camp Travis in the period immediately preceding the epidemic. While the larger epidemic affecting Camp Travis and beginning about March 1, could have been based on the preliminary "flare up" at Camp Stanley, nevertheless the organization suffering earliest invasion and highest incidence had not left Camp Travis. Certain environmental conditions, which apparently had a bearing on the high incidence in the organization will be mentioned later.

Fig. 2 shows that practically all organizations in Camp Travis were simultaneously affected by the epidemic. Fig. 4 shows that Fort Sill, Oklahoma, experienced an epidemic of acute respiratory disease just one month earlier than most of the other stations within the 8th Corps Area. While the remaining stations were not affected at precisely the same time, the graphs show that they were affected at approximately the same time. The epidemic at Fort Sill lasted about the usual length of time, *i.e.*, about a month. It is worthy of remark that the great epidemics affecting the cantonments in 1918, also lasted about a month and showed a symmetrical curve as rapidity of spread and rapidity of retrogression were about equal. From Fig. 2 it can be seen that Infantry Regiment A, presented the highest incidence in Camp Travis. Moreover, one battalion was affected exceedingly more than the others; one company of this battalion had a decidedly higher incidence than any other company in the battalion; and in this company the incidence was explosive, about 25 per cent of the personnel of the company having been hospitalized in a single day. Upon inquiry it developed that this regiment had just commenced rifle aiming practice; the battalion affected had simultaneously discarded the service blouse which interfered with the aiming practice. Part of the aiming was done in the prone position on the ground, which was still cold and somewhat damp. The severest cold wave of the season had just swept down over the camp, and as a result of the cold weather the men were lectured indoors for several days immediately preceding the discarding of their blouses and the beginning of rifle aiming. These facts offer

a reasonable explanation for the exceptionally high incidence in this one regiment. The cold wave referred to came just at pay day, and as Camp Travis is several miles from the shopping district of San Antonio, naturally the soldiers exposed themselves considerably, especially at night, riding to and fro in the open jitney,

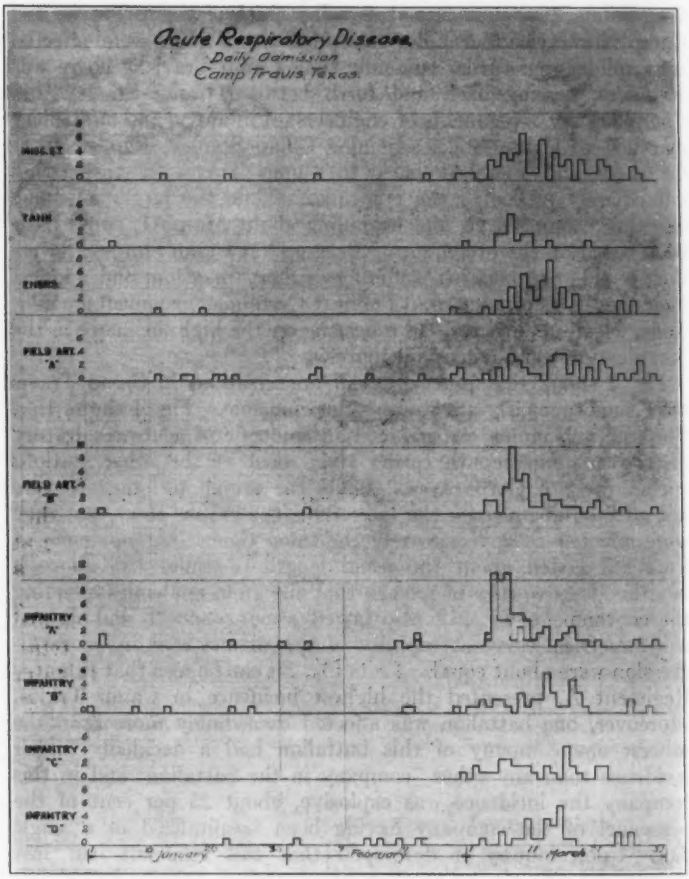

FIG. 2.—Showing daily admissions from acute respiratory disease, first quarter of 1922, among different organizations at Camp Travis, Texas.

which was the main reliance for transportation between camp and city. The severe cold wave, which came at pay day and just when spring training programs were being carried into effect, may have had an influence on all stations within its scope. Fort Sill, Oklahoma, had suffered the severest cold wave of the season imme-

diately preceding the beginning of its epidemic, one month earlier. See Fig. 4 which shows graphs representing the rise and decline of the epidemic at various stations, and which also shows the temperature fluctuations of Lawton, Oklahoma, the nearest weather observation point to Fort Sill. The possible effect of exposure to lowered temperature was investigated so far as 52 soldiers were

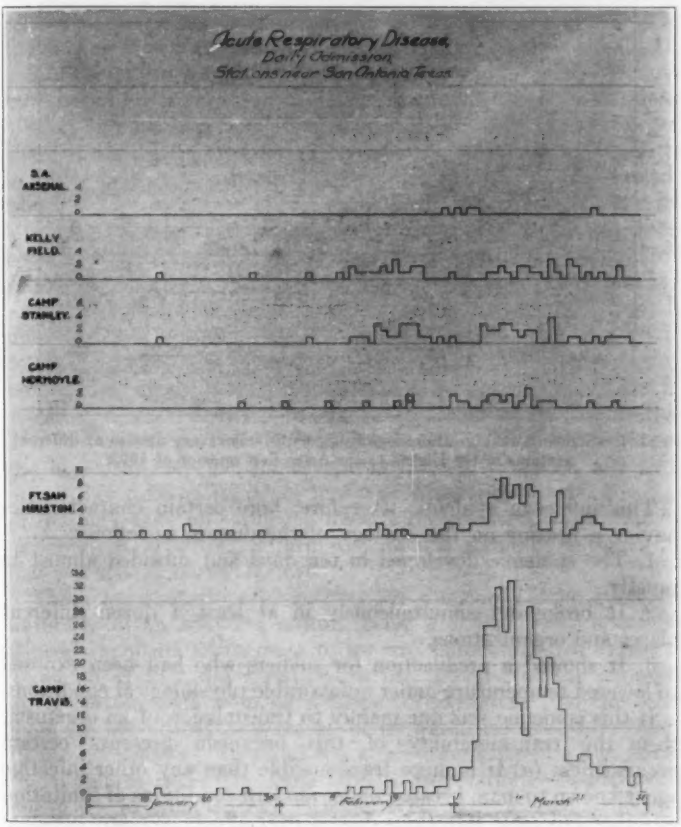

FIG. 3.—Showing daily admissions from acute respiratory disease, first quarter of 1922, at several stations in the immediate vicinity of San Antonio, Texas.

concerned. These men were admitted successively to two wards. Thirty-nine of the 52 gave a history of exposure to lowered temperature.

The name influenza would never have come into being had it not been for the epidemicity which at times characterizes the disease. The individual case of influenza presents no identifying earmarks.

The rapid development and rapid decline of this epidemic correspond to similar traits observed in the epidemics of 1918; hence, this epidemic may be with justice termed influenzal, although the term epidemic bronchitis is more in keeping with our actual knowledge, while at the same time it is more descriptive.

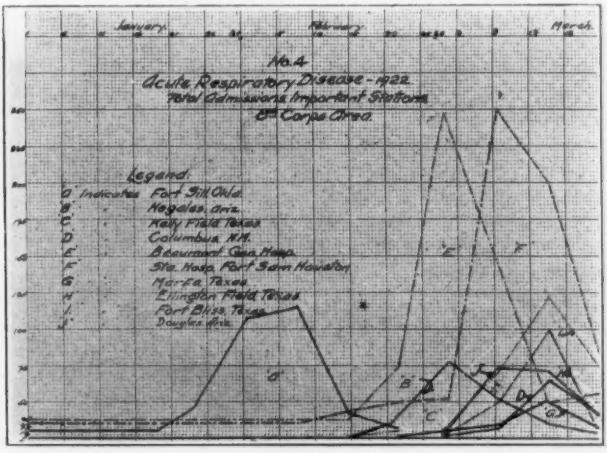

FIG. 4.—Showing weekly admissions from acute respiratory disease at different stations in the Eighth Corps Area, first quarter of 1922.

This influenza epidemic, therefore, bore certain characteristics having a bearing on the etiology of the disease as follows:

1. The epidemic developed in ten days and subsided almost as rapidly.

2. It broke out simultaneously in at least a dozen different places and organizations.

3. It showed a predilection for soldiers who had been exposed to lowered temperature under unfavorable physiological conditions.

If this epidemic was due mainly to transmission of an organism, then the transmissibility of this organism presents certain peculiarities: (*a*) It is more transmissible than any other infective agent known to man, because under modern conditions of sanitation no other epidemic infectious disease ever affects so many persons; (*b*) it is more rapidly transmissible than any other infective agent, absolutely defying analysis. Where we would be prepared for an incubation period of twenty-four to forty-eight hours, influenza travels as fast as man can travel and in addition breaks out in myriads of disseminated foci. While trained scientists were in charge of selected persons whose every movement was regulated by central authority and recorded in black and white, the disease has developed where it would and its origin defied detection as

its spread defied limitation; (*c*) the marvellous transmissibility undergoes rapid extinction with clock-like regularity, regardless of the habits of the people and regardless of sanitary precautions.

The peculiar traits of this epidemic call attention to certain fundamental characteristics of *pneumococci*, the bacillus of influenza. and the other bacterial *flora* which, regardless of any causative influence they may wield, nevertheless are certainly intimately related to the respiratory mucosa. Their continual presence in the air passages is an indication of their adaptation to this habitat, and bespeaks an association between germ and host which must have lasted for ages. During this long period of time, the relations of man and the organism have been marked by an alternation of phase; first, the peaceable or carrier phase; then, the antagonistic or inflammatory phase. No pathogenic strain has ever existed whose being was not, at least to a certain extent, characterized by alternating states; for the pathogenic organism must by definition enter a relatively normal human being and bring about a diseased state. And while it may be granted that the pathogenic organism soon sets up an inflammation in its immediate neighborhood, it must also be recognized that the given organism has resided in relatively normal tissue for a modicum of time. Moreover, many pathogenic organisms are frequently found in healthy individuals, so-called disease carriers, and in these instances the alternation of states on the part of the organism is seen even more clearly, as the organism may live for a time in a healthy carrier, and then may either take up residence in a susceptible person who becomes ill, or may take on virulence toward the carrier himself; and in either event, a setting is furnished for the active or antagonistic phase of the germ's life history.

These manifestations of activity on the part of the germ are naturally of an adaptive nature; being a living creature, its life depends upon its adjustment to its environment, and it is not to be supposed that the variations in the behavior of the organism are a matter aside from its struggle for existence. On the other hand its life history is a record of its past successful adjustment to its environment. And so the alternating phases in the life of the organism are to be looked on as fluctuations of activity in obedience to stimuli from without. Indeed, the asexual division and growth which necessarily characterize the antagonistic phase could not take place unless pabulum were at hand and the environment otherwise suitable.

It is not easy to ascertain just what substances or conditions act as a stimulant to the bacterium to bring on its antagonistic phase, but in general, it is quite clear that the inflammatory state is favorable to the pathogenicity of bacteria. When the respiratory tract is inflamed by measles, the pneumococcus or streptococcus oftentimes becomes awakened to pathogenicity. When the lungs of

the dog are subject to trauma incident to the forcible injection of pneumococcus culture, the culture will provoke lobar pneumonia. In the absence of even slight violence the pneumococci do not show definite pathogenicity toward the lung of the dog. Traumatic pneumonia is a true pneumococcus infection, but the change from quiescence to activity on the part of the pneumococcus is provoked by the inflammatory exudate resulting from the trauma.

Chilling the body surface causes alteration in blood distribution to such an extent that myriads of delicate capillaries within the lung substance are ruptured and some tissue juices and inflammatory exudate are poured out. As a result of the total disturbance in the lung, pneumococci tend to take on virulence, leading to the well known pneumococcus pneumonia following exposure to lowered temperature. Virulence is only manifested in the presence of inflammatory exudate. The invasion of successive lobules of the lung by a pneumonic process takes place from an inflamed locus which serves as a base of operations. Pneumococci often have power to make headway in the lung, once an index of inflammatory exudate is established, whereas they lack the power to inaugurate the first inflammation. As a proof of this, it may be said that the mere introduction of pneumococci into the lung in small amounts simulating natural conditions has usually failed to provoke a pneumonia in experimental animals, but on the other hand it has been possible to provoke a pneumonia in animals by slight trauma plus the pneumococci. During general inhalation anesthesia the mucosa of the respiratory tract is injured and flakes of its epithelium often desquamate off. Some inflammation is associated with the process and the tissue juices and inflammatory exudate tend to provoke quiescent pneumococci present into activity. Mouse peritoneum is very susceptible to pneumococci, and reacts promptly by peritonitis whenever pneumococci are introduced into the peritoneal cavity. That the pneumococcus is stimulated by residence in and on inflamed mouse peritoneum is well known; in fact, it overgrows all other organisms in this habitat. Furthermore, pneumococci grown on mouse peritoneum are more virulent, but this virulence disappears after a few subcultures on artificial media.

Adami says in effect (page 327) "One bacterium cannot cause disease in the normal mammal: when the vitality is lowered it requires several bacteria in close proximity to produce so much discharge that the anti-bacterial substances of the enclosing or surrounding cells become neutralized." I should like to interpret the facts thus:

When the group of bacteria is large enough and virulent enough to provoke an outpouring of inflammatory exudate or lymph, then this latter so stimulates the bacteria that they commence the active or antagonistic phase. Adami says on page 325, "To produce disease we must have a special concatenation of circumstances:

(*a*) The presence of an excessive number of organisms at one surface region; (*b*) congestion of a mucous surface with the passage out of an increased number of leukocytes; (*c*) reëntrance of these at one region bearing the bacteria; (*d*) habitual or recurrent deposits at one spot so as to exhaust the bactericidal powers of the cells; (*e*) temporary or habitual lowered vitality of the cells." There is nothing mentioned in this that is inconsistent with the view that inflammatory exudate exerts the decisive influence toward virulence. On the contrary, the first two considerations uphold the view that inflammatory exudate is the important factor, and even almost seems to shadow forth the same thought.

Bails work on "aggressins" goes further. He produced inflammatory exudate from a pleural cavity by injecting typhoid bacilli. The germ-free inflammatory exudate injected with a sublethal dose of the homologous organism produced an acute lethal result. Bacteria which normally could be destroyed within the tissues survived and multiplied when aggressins were injected with them. The aggressins were produced in greater amounts in severe acute strife between the bacteria and the body cells. Only a little was produced in the test tube. It seems plain here that the contribution of the tissues, particularly the inflamed tissues, to the virulence of the organism is the important factor, granted that the aggressins are produced by the tissues plus the organism, reacting on each other. The organism on artificial media, in the absence of strife, produce almost no aggressins. When mutually inflamed, the two produce aggressins in proportion to the acuteness of the inflammation. This affords rather strong evidence in support of the view that inflammatory tissue juices constitute the aggressins. The idea that the bacteria contribute to the formation of aggressins only when in the antagonistic phase is thoroughly in accord with this view, for the bacteria are protoplasmic and in many respects analogous to cells and it appears reasonable to believe that when excessively stimulated both bacteria and tissue cells throw off particles of an irritating or stimulating nature.

Insofar as the aggressins manifest specificity, stimulating only the homologous organisms, Bails' work does not support the view that inflammatory exudate exerts a stimulating effect on bacteria. Nevertheless the numerous additional instances quoted above show that whenever bacteria are in contact with inflammatory exudate they tend to take on virulence, and hence the view is well supported in spite of any specificity which may have been reported in isolated instances.

The view adduced above to the effect that pneumococci and other bacteria are stimulated by inflammatory exudate so that they acquire virulence and enter their antagonistic phase implies that bacteria are subject to fatigue. No responsive physiological structure (unless it be nerve fiber) can functionate continuously.

A bacterium just removed from the highly stimulating inflammatory exudate characteristic of lobar pneumonia would be expected to undergo a reaction and readily lapse into quiescence. This corresponds with the facts; for while not unknown, it is exceptional to have secondary cases of pneumonia following a virulent case. On the other hand, pneumonia carriers abound around the sick room. It appears to be the rule that bacteria having just passed through a stormy period of residence in an acutely inflamed individual tend to take on their quiescent phase, both in the original host, who thereupon has the crisis and enters convalescence, and in contacts, who thus become carriers. It should be noted that the pneumococcus removed from an active pneumonic lesion and deposited on the mucosa of a normal individual undergoes an abrupt change, an abrupt withdrawal of stimulation. The more severe the case, the wider the gap which the organism must span when taking up life in its new abode. Intense virulence then imposes an additional burden on the capacity of an organism to adapt to quieter surroundings, and hence tends to inhibit immediate transmissibility of the disease.

Transmissibility of the organism is inhibited to a less extent, possibly not at all. If there had ever been an experiment performed which consisted in the repeated transfer of virulent organisms in the antagonistic phase from one acutely inflamed organ (in one animal) to another acutely inflamed organ (in another animal) in series, then according to the view hereinbefore set forth the virulence of the strain should have disappeared. The contrary would be strong evidence against the view. I have learned of no such experiment. Experiments in which the organism to be tested is transferred to a normal animal would not be expected to cause early decrease in virulence, because the natural requirements of the strain are satisfied by the alternating states. It should be noted that the antagonistic phase of a bacterial strain must be assumed to outlast several generations. The peculiar fact that fission occurs without apparently modifying the temporary state of the individual as regards quiescence or activity must be explained on the grounds that asexual division in a less complicated process than mitosis, or it must be left to be explained by further study and experiment. In this connection the observation announced by Flexner[10] is of interest. He observed that poliomyelitis virus (maintained by serial inoculation in monkeys) fluctuated, growing progressively more virulent for several months or years and then becoming less virulent for a similar period. Cecil and Blake have expressed the belief that pneumococcus and streptococcus hemolyticus are powerless to inaugurate a primary inflammation when sprayed into the nasopharynx, but that these organisms readily take hold when *B. influenzæ* have prepared the way and they have well supported their belief with experiments.

The implantation of a secondary invader of severe virulence on a mucosa already inflamed by a primary organism could well be termed "pyramiding of virulence". That is to say, the contrast between acutely inflamed mucosa and normal mucosa might be so sharp that the virulent organism could not step down successfully without passing into the quiescent phase. But when the virulent organism was transferred from a pneumonic lung, for instance, to a trachea or bronchus already moderately inflamed by *B. influenzæ*, it might conceivably survive the change without suffering a reaction amounting to quiescence, and might commence the antagonistic phase anew. The longer the antagonistic phase lasts, the greater the tendency to lapse into quiescence. According to this conception, pyramiding of virulence ought to be common during a widespread epidemic such as the influenza and pneumonia epidemic of 1918, but there is no apparent reason why pyramiding should not occur among different strains of any given species.

In addition, since the tissue cells react in one stereotyped fashion to all forms of irritant, it appears reasonable to believe that pneumococci would be as readily stimulated into the antagonistic phase by inflammatory exudate resulting from heat, cold, trauma, or chemical irritant, as by that resulting from *B. influenzæ*. Hence, the experiments quoted by Cecil and Blake appear to have proved that: "A strain of pneumococci derived from a severe case does not readily continue its antagonistic phase when introduced into normal mucosa of another host, but can be induced to continue its antagonistic phase when implanted upon a mucosa already moderately inflamed by *B. influenzæ*."

In conclusion a word should be said concerning the relation which the interpretation described in the preceding paragraphs bears toward humoral immunity and lowered resistance. Humoral immunity based on antibodies is usually developed during the antagonistic phase of a pathogenic organism's parasitism and it is believed to be based on a special variety of inflammatory exudate. Apparently the body develops no humoral immunity until such time as it is invaded or attacked by an organism and its products. Of course it does not always do so even then. Hence antibody immunity is not necessarily the most important part of immunity but is simply one special adaptation of the body to ward off germ enemies after they attack. Lowered resistance is a much more vague term but the very essence of the term implies "attack from without." Lowered resistance while really only a paraphrase can be assumed to explain all lack of immunity in the face of attack, but to assume any degree of resistance in the absence of attack is gratuitous as well as without foundation.

The present paper deals with certain factors underlying initiation and cessation of attack and hence the field of discussion is not exactly the same as that involved in humoral immunity and lowered

resistance, the question first to be answered is "Does the given strain of organisms attack the body under the given circumstances?" If this is answered in the affirmative then the resistance of the body consisting of humoral immunity and other factors, comes into play. Furthermore if an attack be granted to have occurred, then the subsidence of symptoms should not be attributed to antibodies or heightened resistance without also taking into consideration the possibility of withdrawal of the enemy on account of exhaustion or similar inherent cause.

It is well known that the crisis in pneumonia cannot be satisfactorily correlated with the antibody or bacterial content of the blood, with the pathology of the lung, or with any other changes in the patient himself. An attempt has been made above to bring the critical phenomenon in pneumonia (*i. e.*, the crisis) into line with the past history of the pneumococcus, with the carrier state, and with the epidemiology of milder respiratory infections in an attempt to deduce an underlying principle, as stated.

Summary. 1. This epidemic developed in ten days and subsided almost as rapidly.

2. It broke out simultaneously in at least a dozen different places and organizations.

3. It shows a predilection for soldiers who had been exposed to lowered temperature under unfavorable physiological conditions.

Conclusions. 1. The quiescent phase and antagonistic phase tend to alternate with each other in the life history of facultative pathogenic bacteria.

2. The antagonistic phase occurs in response to stimulation applied to the bacterial organism.

3. Inflammatory exudate furnishes the required stimulation.

4. As regards the disease itself, transmissibility tends to be inversely proportional to virulence.

5. No evidence is seen against the occurrence of pyramiding of virulence within a given species of organism.

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THE USE OF GENTIAN VIOLET IN THE TREATMENT OF EMPYEMA.*

By Robert C. Davis, M.D.,

INSTRUCTOR, DEPARTMENT OF INTERNAL MEDICINE, UNIVERSITY OF KANSAS MEDICAL SCHOOL, ROSEDALE, KANSAS.

My experience within the last year with the treatment of empyema by the aspiration of the seropurulent or purulent exudate, and the introduction into the chest cavity of an aqueous solution of gentian violet has been so satisfactory as compared to the older methods of surgical treatment, especially in those cases in which the exudate is not frankly purulent but a thin seropurulent exudate that I recommend this method of treatment, especially in the early cases.

Empyema is one of the oldest of diseases known. It was known even at the time of Hippocrates and very little progress was made until the last few years in the treatment of this condition. For many years the only facts worth knowing about empyema was that it followed pneumonia; and that its treatment consisted in incision and drainage. The pathology and diagnosis were simple. The operation was simple and for several years empyema seemed to offer no opportunity for more intensive investigation. Now and then an article appeared on empyema, but these concerned themselves merely with surgical technic. In 1914, Wilensky[1] investigated the mortality of empyema at Mt. Sinai Hospital for the preceding ten years; that is, the review that was made was the result of surgical treatment of empyema for ten years, from 1904 to 1914, in empyema resulting before the epidemics of influenza and bronchopneumonia in New York, and showed that even in a good hospital the mortality reached the appalling figures of 28 per cent. And unless one is familiar with the mortality of empyema one is more or less appalled by the statistics of any large hospital in which is treated a considerable number of pneumonias with the resulting empyema. The statistics from the different army camps are also quite a lesson in this respect. And when one has seen the result of operative treatment as soon as the fluid was diagnosed, or by waiting later until adhesions had formed, so as to lessen the amount of lung collapse, one is immediately impressed by the difference in the mortality rate.

Before taking up the use of the aniline dyes in the treatment of this condition it is very necessary that the pathology and pathogenesis of the common empyema is understood. Moschcowitz[2] in his extensive work has shown that there are three stages in the development of empyema.

I. The formative stage.

* Read before the Jackson County Medical Society, Kansas City, Mo., November 28, 1922.

II. The acute stage.
III. The chronic stage.

And in any empyema in which frank pus is obtained it is in this third stage. It is an end product or the terminal even of an infective process in which the first stage is a pneumonia with a small serous pleurisy, and the second is a pneumonia with a greater exudate of seropurulent material; and the third stage is frank pus. In a great number of pneumonias, especially if there is any pleural involvement, there is also a pleural effusion of greater or less amount. I feel perfectly sure that a considerable number of these are overlooked, which is not necessarily a serious thing, because so small an amount of fluid does no harm; in fact, in the pleuresies with acute pain it is a relief to the patient as soon as sufficient fluid forms. This serous fluid becomes infected by an abscess which lies adjacent to the pleura, covering the lung, over the affected area. These abscesses rupture into the pleural cavity, thereby infecting the fluid which is in the pleural cavity. This fluid, when infected, becomes seropurulent and at a later stage purulent. This purulent exudate is later encapsulated due to a fibrinous deposit around the periphery which may be either single or multiple encapsulations. It is very important that we remember the fact in reference to the surgical treatment which is, that a serous and seropurulent fluid is always free while a purulent fluid is encapsulated. In other words, a working rule is, that when the fluid settles out into two layers upon standing, an open drainage should not be done because of there being no, or few, pleural adhesions and the resulting collapse of a large part of the lung. And usually in this stage there is still present a pneumonia. If the purulent exudate has not settled out into two layers the patient has usually recovered from his primary pneumonia, adhesions have formed, encapsulation has taken place and drainage can be accomplished without the resulting lung collapse.

It makes a difference in the mortality varying from 20 to 60 per cent if the patient is operated in the encapsulated or acute stage of the disease. The proper treatment for the acute stage of the disease is aspiration by some closed method insuring that no air gets into the pleural cavity. Every case differs as to the amount of fluid formed and at the rate of formation. We have all seen these cases, especially of streptococcic pneumonia that within a few hours one side of the pleural cavity is half filled with a seropurulent exudate. Others fill very gradually. Autopsy results show that many cases go unrecognized. It was in the first two stages; that is, the formative stage or the acute stage in which pneumonia is still present that Major[3] devised the use of gentian violet treatment.

Before taking up the treatment proper and the indications let me review briefly the use of dyes in medicine. It has been known

for a long time that certain dyestuffs have a selective action on certain bacteria or classes of bacteria. Among the early workers were Rozsahegyi,[4] Shillings,[5] and Koch[6] who showed that various organisms, among them the tubercle bacillus are inhibited in their growth, bacteriostasis, or killed by dilution of dyes. This susceptibility of bacteria to various dilutions of different dyes was pointed out by Rozsahegyi[4] and practical application was made by Drigalski and Conradi[7] in the isolation of the typhoid bacillus. Bacteria were found to vary in their susceptibilities to any particular dyestuff and dyestuffs to vary enormously when used against the different groups of bacteria.

Much work has been done to correlate the chemical structure of dyestuffs and their selective action upon the group relationship in accordance with their dye susceptibilities.

The work of Churchman[8 9 10] who showed the definite relationship between the Gram stain and the susceptibility to dye action, was the later attempt along this line of investigation. In his later work he has pointed out that Gram-positive organisms are more susceptible than Gram-negative bacteria, not only to stains of the pararosalin series, which are used in the staining methods, but also to other groups of dyestuffs as well.

Churchman[11 12 13] used gentian violet successfully in closed cavities in joint infections. He has since shown that besides the Gram-positive organism being susceptible to gentian violet, that the Gram-negative organisms are susceptible to acid fuchsin.[14] Beside the above work; Gay and Morrison[15] working on rabbits produced experimental streptococcus empyema and used a great number of dyes in the treatment of this condition. However, their results were not very satisfactory and their method of application is not the same as used by Major[3] or myself. Other work that has been done is by Waters[16] of the Loomis Sanitarium who reports 2 cases of empyema following artificial pneumothorax for tuberculosis which developed a secondary infection in the plural cavity. One of his patients, especially, shows a very nice response to this treatment. The patient was in a critical condition and the pleural cavity was washed with first a saline injection and later with 1 : 5000 gentian violet and after several minutes the fluid withdrawn. Later 150 cc was left in with remarkable results. The temperature dropped from 105° F. to below normal and the pulse from 160 to 90 and remained there. The treatment was continued the following day, then every other day until the secondary infection was under control. The other case reported by Waters,[16] is that in which there was removed from the pleural cavity 750 cc of thick gray pus showing staphylococci and a few Gram-positive diplococci. After treatment the temperature curve fell below normal within forty-eight hours. Waters[16] ascribes his results to first, the mechanical removal of infected exudate

from the chest and thorough cleansing of the pleural surface; second, the application of an efficient chemical agent by direct and effective contact with this surface. The action of the dyes on pyogenic organism *in vivo* Churchman [8 9 10] characterizes bacteriostatic rather than as bactericidal and his experiment indicates that it has considerable power of penetration and that its effects are manifest in comparatively weak solution.

The experience following the two hasty operative intervention in empyema was so uniformly noted in the influenza epidemic as to constitute a most important single observation made on this subject during the past five years. Rodman[17] noted in his work that the mortality was 45 per cent in the cases in which the method of early operation was employed. Stone[18] reported the mortality of 61.2 per cent. Following a series of such experiences reported from various parts of the country the method of preliminary aspiration rapidly became the method of choice and its value was emphasized particularly in the report of the Empyema Commission[19] and in a more recent article by Moschcowitz.[2] A number of methods of closed drainage also were used. The method of Mozingo[20] irrigating through a catheter; the method of Harloe[21] who inserted a catheter into the chest through which pus was aspirated at various times and which was clamped off during intervals. It was due to the early results of aspiration before the operation that Major[3] conceived the idea of using some sterilizing agent in the pleural cavity.

We have followed rather closely the original technic described by Major.[3] Our technic is as follows: All cases in which a seropurulent exudate in which there are organisms are treated. In all of our cases with seropurulent exudate organisms were found. The chest over the fluid area is anesthetized with 0.5 of 1 per cent novocaine. The aspiration is done with a 50-cc Luer syringe connected to the needle by a piece of rubber tubing two to three inches in length fitted with adaptors to fit syringe and needle. This prevents air entering the chest at the time of disconnecting syringe and needle and also is not likely to injure the visceral pleura and the lung by movements of the patient or by connecting and disconnecting the syringe. A nurse or assistant maintains the position of the needle. The fluid is aspirated until the cavity is almost dry, this to be determined by the patient beginning to cough. One precaution we have observed is that during the first aspiration if there is a large amount of fluid, that we did not take out an unnecessarily large amount, although we have never seen any bad results from slow aspiration. Then one-half as much aqueous solution of gentian violet (1:2500) as fluid removed is slowly injected into the cavity. The fluid is first warmed to body temperature. By a later work of Churchman[22] we know that if the fluid is warmed above body temperature it has more of a bactericidal

value. This fluid is allowed to remain until the next aspiration which should be done from one to five days, depending upon each individual case. During the second and following aspiration a solution of 1:1000 is used. In all there were treated 18 cases of empyema. In none of these was a rib resection done, all clearing up with the use of gentian violet with the technic as described above.

In 4 of our cases at the first aspiration was obtained frank pus. In 2 cases the fluid was serous but organisms were isolated from the fluid at the first examination, the remaining were the typical seropurulent fluid. In 3 cases a chlorazene solution 0.5 of 1 per cent was injected to dissolve the exudate which had coagulated and could not be aspirated through the aspirating needle until dissolved. Two of these cases were seen late in the course of the disease. The first was a girl, aged seventeen years, who entered St. Luke's Hospital with a history of having had pneumonia three weeks previous and being told by her attending doctor she was well. She came in complaining of fever and sweats and a physical examination showed fluid in the right pleural cavity. On aspiration only 300 cc of fluid were obtained with great difficulty, the syringe stopping up numerous times during the aspiration. The mother of the girl refused surgical interference and 50 cc of 0.25 of 1 per cent chlorazene was injected. The following day 600 cc of fluid was obtained and 250 cc chlorazene 0.5 of 1 per cent was injected. Then large amounts of fluid was obtained and the gentian violet treatment carried out, with occasionally using just enough chlorazene solution to keep the fluid thin, 50 cc every other aspiration being about the amount used. In 2 cases a very small catheter was inserted between the ribs by Dr. Elmer Twyman, one because we felt there was fluid that we were not obtaining and the roentgen ray showing a shadow of which we were in doubt, and the patient being seriously sick we decided to try to obtain more pus. The catheter was inserted through a trocar and kept air-tight, irrigation being done through it. The patient had a pyemia manifest by multiple abscesses throughout his extremities and by double acute suppurative otitis media and at a later date double mastoiditis and was operated upon by Dr. O. J. Dixon. As soon as the multiple foci cleared up the chest improved. We do not feel that we gained much, if anything, by the catheter over the ordinary gentian violet method. The infection was Type III pneumococcus from which there is a high mortality and the exudate never reached the thick purulent stage. This patient was in the hospital the longest of the series, being in the hospital one hundred and forty days, and during that time having first a left lower lobar pneumonia, later a pneumonia of the entire right lung, then the empyema, multiple abscesses and double mastoiditis. The second case in which a catheter was inserted by Dr. Twyman was one in

a young boy whom it was almost impossible to treat by aspiration on account of the pain of aspiration. He was also seen late in the purulent stage and chlorazene and gentian violet were used as above.

In 1 case that had a streptococci pneumonia first on the left side, then on the right, developed a lung abscess on the left and and an empyema on the right. In this case he was expectorating quantities of a very foul smelling material and drainage being somewhat worse upon lying on the right side. Physical examination showed dulness at the right base due to fluid and at the inferior angle of the left scapula there was an area of dulness. This was explored with a needle and lung tissue was encountered. Going a bit deeper was obtained 300 cc of foul purulent material that the patient had been expectorating. When the cavity was aspirated the patient said he could feel air being drawn in through his nostrils. The 100 cc of a 1:1000 gentian violet solution was instilled and part was immediately coughed up by patient, the remainder during the next few hours. After two aspirations and instillations the lung abscess ceased draining. The empyema of the opposite side was treated in the usual way and no fluid was obtained after the fifth aspiration. The other cases were the usual cases of seropurulent empyema and all responded. There was 1 patient that has only 1 aspiration and instillation. One had 2 and the others varied from 4 to 14. The patient with the 14 aspirations did not improve after 10 aspirations. About every four days the exudate would reaccumulate and about the same amount would be aspirated. The patient I had previously treated for lues, two years before; he was put on mercury and immediate improvement followed.

The different type of organism seem to have but little to do with the recovery of the patient by this method. The Type I pneumococcus becomes a thick purulent exudate very early, while Type III and streptococcus are seropurulent for some time.

I have also confirmed the observation of Major[3] that, in some of these cases of empyema, soon after the injection of gentian violet some is expectorated by the patient, and in some of these cases two or three days later they may suddenly expectorate some of the dye. This probably explains why some patients choke and cough so readily with the use of Dakin's solution in the pleural cavity, the Dakin's solution being very irritating to the bronchi. In 3 of the cases multiple pockets were found. One feels that such is the case when after an aspiration the temperature fails to fall almost, or down to normal. One should not delay the aspirations until the patient starts to have the profuse sweats. It is realized that this method cannot be universally, successful so one must keep his patient under constant close observation, and must do repeated physical examinations, and know when to aspirate the chest.

It is impossible to predict, after an aspiration, as to what the temperature will do. It always falls, but to a variable degree, depending somewhat upon the resistance of the patient to the infection and upon the amount of the seropurulent exudate aspirated. This seropurulent exudate in some cases is very toxic and after aspirating large amounts, and in some cases a small amount, the temperature will fall almost, if not to normal. The injection of the dye seems to have no immediate effect other than replacing the toxic exudate. I have replaced rather large quantities with the dye and have never yet seen any bad results. There seems to be a very low toxicity of the dye. In this respect gentian violet has an important advantage over most antiseptics and chemical agents in its low toxicity and the absence of symptoms of pleural irritation following applications. Considerable amount of solution can be left in the pleural cavity.

Furthermore, these cases should be recognized during the acute stage while the fluid is seropurulent, as treatment at this stage is much easier because the exudate has not undergone organization and encapsulation. The advantage of this method consists in that a great number of patients with empyemas are treated early in the disease while they still have pneumonias, that they are cured by the time the results of the pneumonia are over, that if one is treating them by the aspiration and instillation of gentian violet during the acute stage they certainly are not going to kill the patient by recommending or doing an open drainage with the resulting lung collapse and death which usually takes place in this acute stage; that the gentian violet is a perfectly safe, as well as sane treatment in that it has a great bactericidal value, that there are no reactions either locally or generally and that the patient improves following the treatment, as is evidenced by our report of 18 cases, none of which had a rib resection. And in the 2 in which a closed thoracotomy was done very little improvement of the syringe method was noted. A large majority of these patients are out of the hospital much sooner than they would be if we had to wait until the pus became a thick pus before doing a rib resection. There are some, as is evidenced by our 1 case, with whom length of time in the hospital is not materially shortened. In some of our cases only 1 or 2 and not more than 4 or 5 aspirations were necessary. The average length of time in the hospital is much shorter than the older methods. The resulting deformity that occurs, especially in young adults, is materially lessened.

Summary. Eighteen cases of empyema are reported treated by the use of aspiration and injection of an aqueous solution of gentian violet one-half as much solution being injected as fluid removed, fifteen cases being treated while the disease was in the seropurulent and early purulent stage and 3 in the encapsulated stage. In the 3 cases which had organization of the exudate

0.25 to 0.5 of 1 per cent chlorazene in small amounts were injected to dissolve the exudate. Novocaine 0.5 of 1 per cent was used locally to anesthetize the skin and peripheral pleura. This method can be used successfully both on the early and late cases, but is especially advised on the acute cases of empyema before encapsulation and while pneumonia is still present.

Conclusion. In conclusion I would recommend the use of gentian violet in the treatment of all acute empyemas, or in all empyemas in which the fluid is seropurulent, which indicates adhesions are not formed and encapsulation has not taken place and pneumonia is still present. The surgical mortality in these cases is especially high. By this method a certain number will clear up without further treatment. If they do not clear up no time is lost and the patient is in a better condition for surgical drainage when the proper time comes.

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REVIEWS.

THE PRINCIPLES AND PRACTICE OF PERIMETRY. By LUTHER C. PETER, M.D., F.A.C.S., Professor of Ophthalmology in Temple University and in the Graduate School of the University of Pennsylvania, etc. Second edition. Pp. 281; 161 illustrations, including 5 colored plates. Philadelphia: Lea & Febiger, 1923.

THE author has in great part rewritten the former edition, giving particular attention to the sections on methods, technic, instruments and charts.

The subject of perimetry is not a new one and constitutes a chapter in text-books on ophthalmology. Fuchs, de Schweinitz, Weeks and others have not neglected this subject in any particular.

This volume contains a bibliography of about fourteen pages, which confirms the fact that many have contributed to this subject and the author must have spent much time compiling the matter to date. Such a book is, therefore, a ready reference in the library of any active ophthalmologist.

Drs. Ferree and Rand have certainly earned an international reputation and are entitled to the thanks of each oculist for their contribution to this subject. It is hoped that eventually their perfected perimeter will be placed on the market.

Speaking of the use of the blackboard and campimeter, Wilbrand states: "This method suffers from the fault that the various parts of the retina are measured from different distances. The greater the distance from the eye, the smaller the retinal image must be, and the less bright the examined object becomes. Therefore, as the same object is used for examining the various parts of the field of vision, different standards of light and size should be used."

Von Graefe first introduced the use of the blackboard for mapping out the fields of vision, and afterward this was much improved by de Wecker. It is now almost entirely discarded for the arc perimeter.

Very few oculists of experience will agree with the author who states on page 93: "It is utterly impossible to make a satisfactory study of the blind spot of Marriott on the perimeter." There are a few corrections which the author should take into considera-

tion when a future edition is called for. In describing Plate IV on page 60, "A" and "B" do not appear in the illustration. There is also a mistake when the author states that the left side of the blue chart is a darker shade of blue than the right half; he certainly means the reverse. The word "perimetric" appears conspicuously throughout the volume, very properly so, and it seems a great pity that in such a neat volume the author is not more meticulous, as he speaks of "physiological," "pathological," "microscopical," "anatomical," so frequently using the final "al," which should be omitted.

It is a pleasure to quote the author when he states that "Perimetry is but the handmaiden of ophthalmology, in itself it is incomplete, but when associated with certain other facts it becomes indispensable." T.

CLINICAL TUBERCULOSIS. By FRANCIS MARION POTTENGER, M.D. Second edition. Two volumes. Pp. 707 and 725. St. Louis: C. V. Mosby Company, 1922.

IN this work the subject of pulmonary tuberculosis is fully considered from various angles. Some of the chapters are highly speculative and theoretical, but in these there is always a practical application apparent. Chapters on pathological changes in tuberculosis, the sources and routes of infection and the factors which predispose to tuberculosis, are clearly and concisely written and give briefly a clear *resume* of accepted beliefs and observations on these points up to the present time.

A long chapter on the nervous system in tuberculosis and the vegetative nervous system in this relation to diseases of the lungs is more novel in its treatment. The author has written widely on this subject in the past and where it is approached in this book his writing is particularly fluent. Some of this matter will doubtless stand the test of time. Some of it, of course, will not. How much is solid cannot at present be known, but there is food for much thought in these chapters.

Close attention is paid to physical examination of patient and particular stress is laid on the noting of changes in structure and tissues outside the chest. Muscle hypertonus and atrophy, trophic changes in the skin and subcutaneous tissues and alteration in chest movement are discussed fully. In the many case histories and clinical records inserted or appended, it will be noted that all these points are routinely observed and recorded in an exceptionally thorough manner.

The chapters on the diagnosis of early tuberculosis are excellent. There is an interesting discussion on the roentgen-ray as an aid to diagnosis and the interpretation of roentgen-ray plates. The

chapter on laboratory methods by J. E. Pottenger gives some useful points regarding the standardization of examinations of sputa. The chapter on "Influenza and Tuberculosis" is well presented, but might have been treated more fully in so exhaustive a volume published just after the influenza epidemic.

Throughout this work a constant endeavor to explain the physiological factors concerned in producing signs and symptoms makes the book interesting and Dr. Pottenger's really authoritative work on physical diagnosis marks the book as one of value.

T.

BRONCHOSCOPY AND ESOPHAGOSCOPY. By CHEVALIER JACKSON, M.D., F.A.C.S., Professor of Laryngology, Jefferson Medical College; Professor of Bronchoscopy and Esophagoscopy, Graduate School of Medicine, University of Pennsylvania. Pp. 346; 114 illustrations and 4 color plates. Philadelphia: W. B. Saunders Company, 1922.

THIS small volume is based on the author's larger and earlier book, *Peroral Endoscopy and Laryngeal Surgery*. A full description of the endoscopic instruments employed in the author's clinic is given and their particular uses considered in detail. The anatomy of the larynx, trachea, bronchi and esophagus are discussed from the standpoint of the endoscopist. The various endoscopic operations are described with remarkable clearness and particular attention is paid to the difficulties encountered in each and the discussion of methods of avoiding or overcoming these difficulties shows the author's wide experience, clear thinking and ingenuity.

To the physician or surgeon wishing to employ endoscopy, Dr. Jackson's authoritative and exhaustive works are, of course, indispensable, but there is much of interest and value for the general surgeon, the laryngologist and the internist to be found in this book. The observations on esophageal diverticulæ are valuable and his work on foreign bodies in the air passages is classic. His descriptions of the physical findings in this condition are probably the best publications on this subject.

T.

INTERNATIONAL CLINICS. Volume II. Thirty-third series. Pp. 304; illustrated. Philadelphia and London: J. B. Lippincott Company, 1923.

THIS number contains three articles on insulin, twelve on medical diagnosis and treatment, eight on surgery, and an obituary on Dr.

J. W. Ballantine. McPhedran and Banting's article on insulin, that on the diagnosis and treatment of allergic diseases by Leeuwen of Holland, and a description of the new disease toularaemia, by Francis, of Washington, D. C., will all appeal to the internist, while "Problems in Surgical Diagnosis, Pathology and Treatment," by Cumston, of Switzerland, is of interest from the surgical standpoint. On the whole, however, it must be said that this number is below the highest standard of *International Clinics*. A.

THE DETERMINATION OF HYDROGEN IONS. By W. MANSFIELD CLARK, M.A., PH.D., Professor of Chemistry, Hygienic Laboratory, United States Public Health Service. Second edition. Pp. 480. Baltimore: Williams & Wilkins, 1922.

IN the second edition of this important work, the author has attempted to keep pace with the rapidly increasing literature on H-ion concentration. The discussion of acid-base equilibria has been accorded fuller treatment and expanded into two chapters. In Chapter V, a very extensive list of indicators has been introduced. More attention has been directed to the simple potentiometer and voltmeter arrangements, the use of which permits H-ion work, where cost prohibits the purchase of complete potentiometer outfits. Nevertheless, the author recommends the more precise instruments, so as to "keep the accuracy of measurement just ahead of immediate demands." New types of apparatus that have received mention are Gillespie's bicolorimeter, Goode's electron tube potentiometer, and the condenser-ballistic galvanometer system for measuring E. M. F. A mathematical treatment of oxidation-reduction potentials has been introduced, based on the more recent concepts of electron interchange. Biochemists should welcome the introduction of discussions of the Donnan equilibrium, cataphoresis, etc., although the subject of colloidal phenomena seems to have been rather neglected. The bibliography has been augmented to include more than 2100 references. O.

PAPERS FROM THE MAYO FOUNDATION AND THE MEDICAL SCHOOL OF UNIVERSITY OF MINNESOTA, 1921–1922, Vol. II. Pp. 716, numerous illustrations. Philadelphia: W. B. Saunders Company, 1923.

THE second volume of collected studies from this celebrated foundation is made up of 107 different papers by almost as many authors. They are mostly based on theses presented by graduate

students toward advanced degrees, and are mostly presented in abstract. Nevertheless, a high scientific level has been maintained and much valuable information afforded. The papers are presented under the 11 headings: alimentary tract; urogenital organs; ductless glands; blood and circulatory organs; skin and syphilis; head, trunk and extremities; brain, spinal cord and nerves; organic and physiologic chemistry; general bacteriology; general miscellaneous; technic. K.

EPIDEMIOLOGY AND PUBLIC HEALTH. A TEXT AND REFERENCE BOOK FOR PHYSICIANS, MEDICAL STUDENTS AND HEALTH WORKERS. IN THREE VOLUMES. VOLUME II, NUTRITIONAL DISORDERS, ALIMENTARY INFECTIONS, PERCUTANEOUS INFECTIONS. By VICTOR C. VAUGHAN, M.D., LL.D., Emeritus Professor of Hygiene in the University of Michigan; assisted by HENRY F. VAUGHAN, M.S., DR. P.H., Commissioner of Health of the City of Detroit, and GEORGE T. PALMER, M.S., DR. P.H., Epidemiologist for the Department of Health of the City of Detroit. Pp. 917; 53 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS second volume of Vaughan's *"Epidemiology and Public Health"* is of equal interest with the first one and demonstrates the author's conception of the wide range of the subject. Many will be surprised at the large number of diseases included, those due to vitamine insufficiences, the various food poisonings (bromatotoxismus) and goiter as well as various intestinal affections, including the parasitic infestations, malaria, filariasis, yellow fever, the trypanosomiases, the kala-azars, tetanus, verruga peruviana, Japanese river fever, tularemia, trench fever, phlebotomus fever and numerous others. The historical sketches are particularly illuminating and quite complete, and the symptomatology in many instances is much more adequately presented than even in most of the recent systems on medicine. M.

DIE MEDIZIN DER GEGENWART IN SELBSTDARSTELLUNGEN. Edited by PROF. DR. L. R. GROTE, Privatodozent an der Universität Halle. Vol. I. Pp. 227; 6 illustrations. Vol. II. Pp. 250; 8 illustrations. Leipzig: Felix Meiner, 1923.

THESE are the first two volumes of a series attempting to present the living history of contemporary German medicine by proceeding "from the person to the subject." Of the six "autoergographs" of the first volume (Hoche, Kummell, Marchand, Martius, Roux,

Wiedersheim) and the eight of the second (Barfurth, Grawitz, Hueppe, H. H. Meyer, Penzoldt, Rosenbach, Schultze, Schultz), only three or four can be said to have acquired more than a national reputation. How different from the names that could have been gathered a generation, or even ten or twenty years ago! In the similar series on philosophy, the contributors are said to be "aware of a certain embarrassment in speaking of themselves. They are overanxious to avoid self-advertisement. 'Americanism' (sic) is discounted." This embarrassment does not seem to have proved much of an obstacle to the authors of this volume. One cannot help being reminded of such projects as "Lives of Eminent Citizens of Squedunk County. Please write your own notice and inform us how many copies you want for distribution among your friends." It does not seem to the reviewer that Germany's attempts to regain her lost leadership in the world of science are furthered by such publications. There is some consolation in the fact that the "tadelloses, holzfreies Papier" will not long withstand the ravages of time. K.

PRACTICAL DIETETICS. By ALIDA FRANCES PATTEE, Graduate, Department of Household Arts, State Normal School, Framingham, Mass.; Former Instructor in Dietetics, Bellevue Training School for Nurses, Bellevue Hospital, New York City. Pp. 646. Fourteenth edition completely revised. Mount Vernon, New York: A. F. Pattee, 1923.

THE popularity of this book is attested by the fact that almost yearly editions have appeared since the initial number. The present edition, however, has been almost entirely rewritten so that in form and arrangement it is practically a new book. If the popularity of the previous editions is a criterion of the merits of the book, it may safely be said that the work is a splendid exposition of the principles of dietetics and of the practice of this most necessary adjunct to proper therapy. M.

CONTRIBUTIONS FROM THE PEKING UNION MEDICAL COLLEGE, PEKING, CHINA. Volume II, 1922. Peking, Peking Union Medical College, 1923.

THE second volume of the compilation of medical contributions to current literature from the pen of the various workers at the Peking Union Medical College is a very splendid example of what may be done by those working with enthusiasm and zeal even when handicapped by the obvious difficulties which are met with in a

semicivilized community, as we understand it. The contributions are catholic in their aspect; eye conditions, as would be expected, take up a goodly part of the work; but laboratory studies, parasitology and similar subjects are dealt with. In addition to the contributions of the local staff of the Peking School there are also included in the work the papers delivered at the dedication ceremonies of the Medical School in 1921. M.

THE DOMINANT SEX. By MATHILDE and MATHIAS VAERTING. Translated from the German by EDEN and CEDAR PAUL. Pp. 289. New York: George H. Doran Company, 1923.

THE motive for this work is the effort of the authors to prove that either sex may be the dominant or the stronger one and that if either sex is truly dominant the characteristics which we know as feminine or masculine vary according to the sex which is the ruling one. Throughout their work by analogy with earlier races and the comparison of the animal kingdom they attempt to show that in those races in which the female sex is the ruling one, the male becomes entirely a subsidiary partner. The arguments of the authors are for the most part well taken. The reviewer does not feel that they have proved their main point, which is that in the course of the present civilization sooner or later there will come the equality of the sexes; the dominance of man over woman will no longer persist. In a criticism of the work it would seem that the whole force of the authors' arguments were invalidated by trying to show that in the animal kingdom the dominant sex is the female. It would thus seem that, as an incorrect statement of fact is one of their strongest arguments, others of their arguments may not be entirely true. M.

OPTOTYPES. SEVENTEEN TEST LETTERS AND PICTOGRAPHS. By GREEN and EWING. Published by the C. V. Mosby Company, St. Louis, Mo., 1923.

THESE seventeen cards of test letters and pictographs for measuring the acuteness of vision, by Green and Ewing, are the very best and ideal of their kind.

Each card measures fourteen by seven and a half inches, making them very convenient for office use, especially so as each one is punched for binding.

The reviewer has no unfavorable criticism to make, but, on the contrary, recommends these valuable accessories, especially to those who do eye-testing in institutions for the deaf and dumb,

feeble-minded and illiterates. Therefore, these cards are not in every-day use in the office of the active ophthalmologist.

An immense amount of work and expense has been given by the authors and publishers, who are to be thanked for this contribution to ophthalmic science.

ANNALS OF ROENTGENOLOGY. A SERIES OF MONOGRAPHIC ATLASES. Edited by JAMES T. CASE, M.D., Ex-President of the American Roentgen-ray Society. Volume III. Digestive Disturbances in Infants and Children Roentgenologically Considered. By Charles Gilmore Kerley, M.D., and Leon Theodore Lewald, M.D. Pp. 81; 166 illustrations. New York: Paul B. Hoeber, 1923.

THIS is the third of the monographic atlases in the *Annals of Roentgenology* series, and it is divided into two parts. The first part, prefaced by a note on the Surgery of Infants, by Dr. William A. Downe, is a discussion of the digestive disturbances of infants and children. The second is made up of 117 roentgen-ray studies of the conditions mentioned in the first part. In these studies are included the history, the roentgen diagnosis, with the lesion or abnormality clearly indicated on the handsome illustrations, and the result of treatment.

This volume is a welcome and valuable addition to the relatively scarce literature of its kind, and one that truly fulfils its purpose as a diagnostic guide. Z.

PHYSIOTHERAPY TECHNIC: A MANUAL OF APPLIED PHYSICS. By C. M. SANSOM, M.D. Pp. 443; 85 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS book deals with the thermal, chemical, mechanical and electronic methods of treating disease and conditions resulting from disease and trauma. Indications for the use of and the technic of application of these modalities are discussed very thoroughly and in detail. While the author's claim of brilliant results in the treatment of locomotor ataxia, and that 'the treatment of hayfever by physical means comes near to being specific,' must be accepted with some reservation until the efficacy of these means has been more universally proved, the work contains much useful information, especially for those who are engaged in reconstruction work.

Z.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

PROFESSOR OF MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND,

AND

ROGER S. MORRIS, M.D.,

TAYLOR PROFESSOR OF MEDICINE IN THE UNIVERSITY OF CINCINNATI, CINCINNATI, OHIO.

The Neutralization of Tetanus Antitoxin with Nucleic Acid.—DOYON and DUFOURT (*Compt. rend. Soc. biol.*, 1923, **88**, 1244) have discovered that nucleic acid is able to neutralize tetanus toxin *in vitro* within five minutes after the two substances are brought together in solution. If the mixture be injected before the five-minute period has elapsed, then some of the toxin is still active, its toxicity being inversely proportional to the time that has elapsed. Smaller quantities of the acid merely delay the tetanus and death. Protection *in vivo* is less effective, although death may be delayed, the prolongation of life depending on how closely the acid injection followed that of the toxin. Tartaric acid is less active in neutralizing the toxin, while sodium nucleate is entirely inactive. Nucleic acid precipitates the toxin and certain other elements from culture media.

Value of Phenoltetrachlorphthalein on Estimating Liver Function.—PIERSOL and BACKUS (*Arch. Int. Med.*, 1923, **31**, 623) describe a method of performing the phenoltetrachlorphthalein liver function test that adds considerably to its value as a clinical procedure. A duodenal tube is passed so that the tip rests in the second portion of the duodenum, and a steady drip from the outer end is initiated by aspiration and is maintained by having the patient drink a glass of water every half hour. The dye is injected as soon as a steady drip of bile-stained fluid is obtained, and the appearance time of the first dye is noted, as well as the time of its maximum intensity. Their principal contribution lies in their quantitative estimation of the amount of dye thus excreted by the liver for each half hour of a two-hour period following the injection. These estimations were made colorimetrically after first removing the

bile salts by precipitation and filtration. This quantitative feature of the test makes it, in the opinion of the authors, as useful in testing the functional capacity of the liver as is the phthalein test for the kidney. In a series of 50 cases tested, they found the delay in the appearance time of the dye to be proportional to the decrease in the output. In grossly pathologic livers the appearance time was twice as long as normal (23.2 minutes as compared to 11.6 minutes), and the dye output averaged but one-eighth of that in normal cases (2.71 mgm. as contrasted with 22.4 mgm.). This method substitutes the use of the duodenal tube in the place of withdrawing blood for examination to determine the dye excretion.

Amebic Bronchitis without Abscess.—PETZETAKIS (*Bull. et mém. Soc. méd. d. hop. de Paris*, 1923, **39**, 1229) reports 2 cases of pure amebic bronchitis. Each occurred in Egyptian males, laborers, in the fourth decade and was observed in the Greek Hospital of Alexandria. The symptoms were those of a mild bronchitis with cough and expectoration. The symptomatology was not characteristic in any way. The examination of the lungs showed no abnormality except the presence of rales, chiefly dry, which were somewhat generalized in one patient, localized about the angle of the left scapula in the other. There was no evidence of infiltration of the lungs, the liver was normal, there was no dysentery; one patient had had 3 to 4 stools daily for several weeks. The sputa were mucous, glairy, tenacious and streaked with bright red blood. In each case, actively motile *Entameba histolytica* were observed in large numbers, as well as the cysts. Both patients were promptly cured by intravenous and subcutaneous injections of emetin, 0.06 gm. The author has observed 3 more cases but they are still under treatment and are not reported here.

The Effects of Quinidine upon Paroxysms of Tachycardia.—ILIESCU and SEBASTIANI (*Heart*, 1923, **10**, 223) present a review of the reported cases of paroxysmal tachycardia—both auricular and ventricular—treated with quinidine, and report the results obtained in 2 cases of their own. They find that cinchona alkaloids are capable of slowing a heart which is affected by simple paroxysmal tachycardia. The action cannot, however, be looked upon as constant, as it failed to appear in 2 cases reported by Singer and Winterberg and in 1 of the author's cases. They believe it possible that the reaction would be constant were the doses of the drug increased. The preliminary slowing of paroxysmal tachycardia and the subsequent and abrupt transition to normal rhythm observed in many reported cases suggest that paroxysmal tachycardia may depend essentially upon circus movement, as do flutter and fibrillation. In cases responding favorably to quinidine, a single dose of 0.4 to 0.6 gm. by mouth has released the heart from the paroxysm. The transition to the normal rate is usually abrupt, though it may be gradual, as in the authors' case.

Diabetes and Insulin.—In the discussion on this subject at the annual meeting of the British Medical Association, Section on Medicine, BANTING (*Brit. Med. Jour.*, 1923, **2**, 446) gave the opening address, in which he recounted first the story of the research which led to the

preparation of insulin. He then takes up briefly the well-known facts about insulin; its preparations, in the laboratory, reduce the blood sugar to normal or less, render the urine sugar-free and by its means the depancreatized dog could be kept alive three times as long as without this organ. The clinical work has been done in Toronto by Graham, Campbell, Gilchrist and Fletcher, who find at the present time there is no fixed method of managing diabetic patients. Their habit is to admit the patient to the hospital for three weeks' training in routine and working out of tolerance if the case is at all severe. The patient is put upon the usual diet for twenty-four hours. He is then put upon a basal requirement diet of 4 grams of protein per kilo body weight. The remaining calories are made up of carbohydrate and fat in ratio of 1 to 1.3. This diet is continued for three or four days. In mild cases the patient usually becomes sugar-free. In the more severe the sugar output becomes constant. If the patient becomes sugar-free the carbohydrate is raised. If he could take 500 calories over and above the basal requirements insulin was not given. One unit of insulin is held to metabolize 2 to 2.5 grams carbohydrate, but this varied in different cases and in the same case at different times. The presence of infection required less. In mild cases one unit of insulin might metabolize 5 to 6 grams of carbohydrate. The initial dose should not be sufficient to make the patient sugar-free, five units usually being given to start with unless the patient is comatose. It is given an hour before meals and never more than once a day. By keeping the patient sugar-free on diet and insulin there apparently is a tendency on the part of the pancreas to produce insulin, as evidenced in many cases by the increased tolerance after insulin treatment, particularly in those cases adequately controlled by diet.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL AND NORTHEASTERN HOSPITALS.

Space Compensating Function of the Cerebrospinal Fluid: Its Connection with Cerebral Lesions in Epilepsy.—DANDY (*Bull. Johns Hopkins Hosp.*, 1923, **34**, 245) says that in a series of operations for the relief of epilepsy a number of changes have been found with considerable uniformity. These are: dilatation of the ventricles, collection of fluid in the brain substance, softening of the brain in association with these collections of fluid, areas of induration in the brain (fibrosis or gliosis), changes in the meninges, and congenital malformations. It is believed that these are evidences of actual cerebral lesions (end-products of repair), and the frequency of the findings leads to the con-

clusion that there is a pathological basis for so-called idiopathic epilepsy in a large proportion of the cases. Confirmation of this view is obtained by means of ventriculography, which in a certain proportion of cases shows acquired or congenital distortion of the ventricles.

Studies on Tumor Formation (Heterotopic Tumors).—NICHOLSON (*Guy's Hosp. Rep.*, 1923, **73**, 298) says that an epithelial tumor is heterotopic only when some or all of its cells belong to a different histological type from that of the organ in which it has undergone its development. The best-known examples are found in the squamous-cell carcinomata of mucous membranes lined by glandular epithelium. Heterotopic cells constitute either the whole or only a part of the parenchyma of these tumors. Their histogenesis is to be explained by metaplasia, a de-differentiation, followed by an atypical re-differentiation of differentiated cells, and not by displaced cell-rests or other congenital malformations.

Köhler's Disease of the Tarsal Scaphoid.—GREENWOOD (*Lancet*, 1923, **2**, 205, 274) says that a history of trauma could probably be obtained in every case from parents of average intelligence, especially if the period inquired into is allowed to stretch as far back as two years. The author feels in the light of his own case that the child is subject to mild latent tuberculosis. This bone, being the keystone of the arch, is most subject to strains, stresses and blows. The early stage, evidenced by a rarefying osteitis, gives rise to such trifling clinical signs that no complaint is made and the disease usually escapes notice. When neighboring bones are involved, the case is diagnosed as frank tuberculosis of the tarsal bones. But should resolution occur and a reparative sclerosis take place either no diagnosis other than sprain or incipient flat foot is made, or a roentgen-ray examination is made and the condition found is called Köhler's disease. The author's case is a borderline case, since actual necrosis to a very limited extent had occurred.

Syphilis of the Stomach.—LARIMORE (*Surg., Gynec. and Obst.*, 1923, **37**, 133) says that gastric syphilis manifests a variable symptomatology, a chemistry and roentgen-ray findings that cannot consistently be of any other well-recognized gastric disease. The presence elsewhere of other undoubted signs of syphilis is a very large support to the diagnosis of syphilis of the stomach, and when absent great care must be used in making that diagnosis. Successful medical treatment is diagnostic only in early gastric syphilis. Restoration of normal gastric motility cannot be expected in well-advanced gastric syphilis. Surgery is indicated in late cases with permanent impairment of the gastric motor function. It is indicated by the clinical course and by the roentgen-ray findings. Resection of the prepyloric stomach is the preferred operation.

Tuberculosis of the Epididymis.—MAXEINER and WALDSCHMIDT (*Minnesota Med.*, 1923, **6**, 492) say that in a series of 15 cases, 10 showed extragenital tuberculosis before operation. The average duration of symptoms was nine and one-half months before operation. Pain, which is usually considered negligible, was present in 13 cases. In a

large majority of cases the first symptoms were noted in the lower pole. Two-thirds of the cases were of bilateral involvement. In one-third of the series, one testicle was so badly involved that it had to be removed. Eight cases report improvement, 7 are unchanged. Local anesthesia and primary closures were employed to prevent spread of involvement and sinus formation respectively.

Flow of Lymph from Ileocecal Angle and its Possible Bearing on the Cause of Duodenal and Gastric Ulcer.—BRAITHWAITE (*Brit. Jour. Surg.*, 1923, **11**, 7) says that cases showing actual and obvious pathological extension by direct lymphatic connection from the ileocecal angle to the region of the pyloric end of the stomach are numerous. A suggestive pigmented gland case was cited in full in the article. Moynihan in an abdominal operation found a mass of tuberculous glands in the ileocecal angle, a complete chain up to the third part of the duodenum, and in addition, a chain running along the common bile duct. A remarkable case was cited by Gordon Taylor, which developed symptoms of perforated gastrojejunal ulcer in the line of anastomosis of a previously performed gastroenterostomy. Operation revealed the perforation with a generalized peritonitis. As a part of a routine examination the appendix was examined, and found to be in the stage of acute gangrenous inflammation. This case would suggest infection of the posterior wall of the stomach from a flow of highly infected lymph.

Retrograde Intussusception of the Small Intestine after Gastroenterostomy.—DRUMMOND (*Brit. Jour. Surg.*, 1923, **11**, 79) says that retrograde intussusception of the small intestine is now a well-recognized complication following gastroenterostomy. Fourteen cases have been recorded. The type of gastroenterostomy performed has nothing to do with the occurrence of the ascending intussusception. In all probability the ascending intussusception is caused by too rapid emptying of the stomach, causing irritation of the jejunum and setting up of antiperistalsis. Diagnosis is straightforward and should, now that the condition has been recognized, be easily made. The history of a previously performed gastroenterostomy, often of many years' standing, followed by sudden griping epigastric colic, vomiting of blood, often a palpable tumor in the left hypochondriac region, with absence of rigidity, distention and acute tenderness, suggest the diagnosis. The treatment of the condition is immediate operation. A reliable preventive treatment has not been suggested.

Loose Bodies in Joints.—HENDERSON and JONES (*Jour. Bone and Joint Surg.*, 1923, **3**, 400) say that osteochondromatosis of the synovial membrane is one of the causes of osteocartilaginous loose bodies in the joints and probably the sole cause of the bodies in the bursæ and tendon sheaths. They believe that the condition should be classified as a benign neoplasm. Trauma is a secondary factor. One of the authors' cases was associated with a malignant chondrosarcoma in the lower end of the femur. No malignancy was discovered in the knee-joint. Removal of all the bodies relieves the patient in the majority of instances. Amputation or resection was not found necessary for synovial osteochondromatosis.

Experimental Incision in the Cadaver for Drainage of the Ankle-joint.—DAVID (*Jour. Bone Joint Surg.*, 1923, **3**, 481) says that the ankle-joint may be divided into two compartments by an imaginary line passing transversely through the center of the malleoli. The posterior compartment is formed by the posterior surface of the trochlea, the anterior being formed by the relaxation of the anterior ligament over the neck of the astragalus. Experimental work on a number of cadavers proved that the posterior external approach was a reliable and safe one. The joint cavity is easily accessible by this route, and with the foot dorsiflexed to a right angle, evacuation of the fluid was complete.

An Electrochemical Interpretation of Shock and Exhaustion.—CRILE (*Surg., Gynec. and Obst.*, 1923, **37**, 342) says that there is much evidence in support of the conception that man and animals are electrochemical mechanisms constructed on the pattern of the constituent cells, each one of which in itself is an electrochemical mechanism. The author outlines the various electrical principles and phenomena noted in cellular physiology. The nucleus is positive, the cytoplasm negative. The brain as compared with the liver is positive. By his hypothesis the brain is the positive pole, the liver the negative, the connecting lines the nerves, the salts in solution, the electrolyte. Sleep is interpreted as a period of recharging of batteries decreased by activities of the day. The theory would interpret that there is no surgical shock when the state of negativity is maintained by the exclusions of stimuli.

Renal Hemorrhages (Postoperative).—JIANOU (*Jour. d'urologie*, 1923, **15**, 350) says that the conservative operation of nephrotomy is not without danger or complications. There are two varieties of bleeding after this operation: primary, occurring within several hours of operative procedure, which is arterial in character; and secondary hemorrhage, occurring six to twelve hours after operation, which is either venous or arterial in nature. Several authors are quoted who think infarct with subsequent processes of infection are the causal factors in late hemorrhages. The author thinks that the hemorrhages are due to section of intrarenal vessels, with infection as a sequel. He recommends the deep lock-stitch suture through the entire area sectioned.

Brain Abscess.—KEEN (*Arch. of Surg.*, 1923, **7**, 297) says that brain abscess in general is difficult of treatment: Abscess of the frontal lobe of the brain has been recognized before death in only about one-half of the reported cases. The high mortality indicates the need of a more careful study of such cases. Persistent headache with sustained leukocytosis and especially the presence of retinal changes indicative of pressure in cases of drained frontal sinusitis or ethmoiditis indicate exploration. Exploration by the two-stage operation through a sterile field may be indicated. Direct drainage with a minimum trauma should be established and should not be discontinued until all symptoms have subsided. It is of paramount importance to drain a brain abscess for too long rather than too short a time.

The Transfusion of Unmodified Blood.—Brines (*Arch. Surg.*, 1923, 7, 306) says that a greater degree of care and accuracy should be exercised in choosing donors. Sodium citrate is harmful chemically, biologically, and physically in blood transfusions, and some fatalities have followed its use. Reactions are fewer and milder following the whole blood method than following the citrate method. The Unger method seems to be the most simple and most generally successful for the giving of blood directly. This method ensures promptness, as no time need be consumed by preliminary details or arrangements. With the proper listing of professional and semiprofessional donors, it should be possible to perform a direct transfusion in any part of a large city, within notice of one hour.

Upon Operation for Ischiorectal Fistula.—Kirchmayr (*Zentralbl. f. Chir.*, 1923, **25**, 993) outlines the faults and direful complications of fistula operations, with incontinence of gas and feces. The author's experience had been first to spare the sphincter, and if cut, to reunite it by suture. In removing the fistulous tracts, especially when attended by marked infiltrate, the wounded areas healed and filled with granulations extremely slowly. Fat-flaps were dissected out and inserted into the cavity. Very excellent results followed these measures. The author has found the fat-flaps useful in separating concomitant fistulæ of the rectum and vagina.

PEDIATRICS

UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,

OF PHILADELPHIA.

A Seasonal Tide of Blood Phosphates in Infants.—Hess and Lundagen (*Jour. Am. Med. Assn.*, 1923, **79**, 2210) have made a most interesting investigation to show this. In their series during 1921 in the summer the phosphate content of the blood was 4.34 mg. per cent, which is within the normal for the Bell and Doisy method. Further data were not available for 1921 until December when it was found that the average had fallen to 3.92 mg. per cent. Monthly examination, some 300 in all, on 60 infants, demonstrated a steady decrease of the inorganic phosphate content, the lowest ebb being in March. This level would have been still lower had it not been for the fact that whenever the phosphate content was found to be as low as 3.75 mg., the child was given either sun treatment or irradiation from an artificial source. It was found that the blood test furnished a valuable criterion as to when heliotherapy should be instituted. In April the tide began to rise, ascending markedly during May, and rising to almost a normal level during June. It seems probable that this seasonal tide with its summer flood and winter ebb occurs to a greater or to a less degree in most bottle-fed babies living in large cities. These babies were outdoors every fine day bundled up in the usual manner with only the

faces showing. Their diet was far better than the average. The authors are unable to state how breast-fed babies react to tidal blood variation. They believe however that these also show a seasonal variation from the fact that 50 per cent of well nourished breast-fed babies coming to their clinic show clinical evidence of rickets at the end of March. The seasonal variation evidently indicates that the chemical constituents of our blood is not constant for all periods of the year. This probably holds true of other tissues. Marked fluctuations of this character may be discovered only in young children, in whom the body has to make provision not only for metabolism associated with maintainance, but also for that demanded by rapid growth, a mechanism which necessarily involves a tendency to wider deviations from the normal. It is quite possible that the phosphate blood tide is only one of the many seasonal variations that take place in the body. Undoubtedly climatic conditions exert a pronounced influence on general nutrition. It is also quite possible that chemical alterations of the tissues, induced by seasonal meteorological variations, may exert an influence not only on nutrition but also on infection. The low content of inorganic phosphate that occurs in early spring and is closely associated with rickets may play a role in the susceptibility to infection which accompanies this disorder. Seasonal alterations of the blood may bear a relationship to the vagaries of incidence of the epidemic diseases.

The Mechanism and Fundamental Causes of Epilepsy.—ROSETT (*Arch. Neur. and Psychiat.*, 1923, **9**, 689) found in his investigations that a physiologic reaction in normal man and animals exists, composed of the following connected train of phenomena: a temporary reduction, disintegration or extinction of the cerebral functions; a tonic contraction of the entire skeletal musculature, with a certain predominance of the extensors, adductors and pronators; the consequent fixation of the joints resulting in the posture characteristic of the state of decerebrate rigidity; clonic muscular contractions or alternating contractions of antagonistic groups of muscles; recovery, marked by symptoms of integration of the disintegrated cerebral functions and a state of general exhaustion. This reaction occurs on exposure to the action of a stimulus requiring sudden movement on the part of the organism, or the narrow focussing of attention and in connection with certain functions such as sleep, defecation, sneezing, coughing, parturition. The mechanism of this reaction is to be found in certain anatomic structures and physiologic functions underlying the production and distribution of muscle tonus in the nervous system. The biologic purpose of the reaction is the automatic fixation of the relatively distal segments of the body and limbs. The reaction is characterized by a periodicity of occurrence. The phenomena which constitute the normal reaction described being in a great number of particulars the same as those which constitute the epileptic paroxysm, might be suitably called the normal epileptoid reaction. This is elicited with greater ease under the influence of the same agencies which cause an exaggeration of the epileptic paroxysm. An example of such an agent is caffeine. On the other hand, influences which tend to hold the epileptic reaction in abeyance, such as bromides and phenobarbital, have the power to diminish the manifestations of the normal epileptoid reaction. Any factor, which operates

permanently to cause large periodic suspensions of the highest nerve functions, whether that factor be a brain tumor, a poison in the blood, a peripheral irritation on an inherited defect will tend to bring about the clinical picture of the epileptic paroxysms.

The Treatment of Acute Poliomyelitis.—Adcock and Amoss (*Jour. Am. Med. Assn.*, 1923, **81**, 474) report a case of poliomyelitis in which they used intravenous injections of hypertonic solution and convalescent human serum intraspinally. In former experiments they found that monkeys given convalescent human serum intraspinally or intravenously and hypertonic salt solution intravenously showed marked improvement as compared to controls. By the shrinking of the central nervous tissues after intravenous injection of hypertonic salt solution more space is available in the subarachnoid space for the reception of large amounts of convalescent serum. This is an advantage as the serum is at best weak in antibody content, and correspondingly large amounts must be injected. The beneficent effect of the change of the tonicity of the blood with the marked decrease in the volume of the brain and spinal cord, is to reduce the inflammatory edema of the cord. Their experiments have not advanced sufficiently to warrant the statement that edema is entirely due to osmosis. The main possibility of the beneficent result of this method lies in the fact that the intravenous injection of hypertonic solution brings about an aspiration of serum from the subarachnoid space into the perivascular system, thus ensuring a more intimate contact between the main lesions of poliomyelitis and the serum, which can be regarded as a distinct advantage in local specific therapy. There is another possibility in connection with the employment of this method. It is possible to administer enough hypertonic solution, approximately 1 gm. of sodium chloride per kilogram of body weight, to cause cerebrospinal fluid pressure to fall from 120 mm. of water to 90 mm. of water without damage. This loss of fluid within the central nervous system is replaced afterward by an increased passage of fluid from the blood stream to the cerebrospinal fluid, normal pressure being restored within a few hours. On the hypothesis that this increased flow of fluid would facilitate the passage of serum from the circulation to the fluid spaces of the central nervous system, the intravenous injection of immune serum one or two hours after the injection of the hypertonic solution is recommended. The case reported conforms to the type of Landry's paralysis seen in epidemics. In such a case the prognosis is usually grave. Whether the intravenous injection of hypertonic salt solution stayed or slightly cleared the edema of the cord, or brought the convalescent human serum nearer the site of inflammation, or only made it possible to inject more serum intraspinally without danger of pressure, is not clear.

Health and Nutrition Work among Children of the Preschool Age.—Bacon (*Atlantic Med. Jour.*, 1923, **26**, 606) at the Starr Center Dispensary has found that the Woodbury or Baldwin tables are at present the best indices of nutrition for children between the ages of two and six years. Ideal standards must be established. Once these are decided upon, measurements of various groups of children must be made

according to standard regulations. The class method combined with personal interviews with those in the class has given encouraging results with children of the preschool age. The success of a class depends largely upon the ability and the ingenuity of the doctor and his assistants. Evidence of value of nutrition work among children of the preschool age are shown by the formation of health habits which stand the test of time; by signs of physical improvement such as the correction of defects, as correction of heart action, correction of constipation, gain in weight and height, and decreased tendency to become ill; and a definite tendency on the part of the child to adapt himself to a social and hygienic environment.

The Value of the Toxin (Antigen) of Rhus Toxicodendron and Rhus Venenata in the Treatment and Desensitization of Patients with Dermatitis Venenata.—STRICKLER (*Jour. Am. Med. Assn.*, 1923, **80**, 1588) says that in the treatment of dermatitis venenata due to poison ivy or poison oak, the toxin (antigen) method of treatment constitutes the best method of procedure. Counting the unsuccessful and doubtful results in his series of 356 cases, there were noted 19 cases, slightly more than 5 per cent, in which failure or only slight improvement resulted. These results were obtained without the additional use of local applications. Relief was obtained in twenty-four hours after the institution of the treatment. Only occasionally, and then in very severe or generalized cases, does a forty-eight-hour interval elapse before relief is obtained. Cure is obtained within from four to five days after the institution of the treatment. In the desensitization of highly susceptible patients the results seemed to be encouraging. While this series was not sufficiently large to arrive at positive conclusions, the results were sufficiently satisfactory to at least warrant a trial in such individuals. The method of desensitization is a rational one, and it is based on the principles that have been successfully applied to the desensitization of other disease conditions. Considering that in the past no hope of prevention could be held out for these constant sufferers from poison ivy, and realizing the great suffering and dread that these patients undergo, there seems to be more than an ample justification for the employment of this method of desensitization. The treatment is simple and can be carried out with ease, and if future results justify past experiences, this treatment should prove a great blessing to the susceptible persons. The method is a combination of intramuscular and oral administration.

OBSTETRICS

UNDER THE CHARGE OF

EDWARD P. DAVIS, A.M., M.D.,

PROFESSOR OF OBSTETRICS IN THE JEFFERSON MEDICAL COLLEGE, PHILADELPHIA.

Repeated Dystocia from Fetal Anomaly in Successive Pregnancies.—MCDONALD (*Am. Jour. Obst.*, 1923, **6**, 82) describes a remark-

able case where a patient had transverse position and the same abnormalities in the fetus in successive pregnancies. The mother's age was twenty-eight years, and for two generations the family history gave no record of the birth of a deformed child. Before coming under observation she had two pregnancies resulting in premature labor, one child living but a few hours, the other stillborn. The statement is positively made that there was no external deformity in either of these children. There was no history of previous infection or acute disease in the mother, and the Wassermann reaction in husband and wife a year previously had been negative. Pregnancy proceeded until about the seventh month, with great distention of the abdomen and evidence of excessive fluid. At labor a small foot protruded with six toes. On endeavoring to extract the fetus the abdomen was found so enormously distended that it was necessary to rupture the abdominal wall of the fetus, when a very large quantity of clear fluid was expelled. A small fetus was easily extracted. There was practically no amniotic liquid. There was transposition of viscera, abnormality of the bladder and hydrocephalus. About two years later, the same patient gave a 1+ Wassermann reaction. She was treated with arsphenamine and mercury. At three months' pregnancy there was bleeding and pain with the discharge of no mass or clots, and pregnancy went on until heart sounds were heard and movements were felt. At about seven months labor developed; birth was accomplished with the head extended, brow presentation, face anterior. The child died soon after birth. On examination, the same abnormalities essentially were present which were found in the preceding pregnancy. The sex of the second child differed from that of the first. This case presented four types of abnormality: (1) The unusual number of fingers which were webbed; (2) transposition of viscera; (3) abnormal development of the urinary tract with hypertrophy of the bladder wall and patent urachus; and (4) dropsy. So far as the condition of the fingers is concerned, this has been traced in some families through four generations. As regards the frequency of malformation, it has been estimated that spontaneous abortion occurs in 20 per cent of all pregnancies. In all abortions from 40 to 60 per cent are associated with a pathological condition in the product of conception. Such abnormalities occur during the first two months of pregnancy, before the development of the placenta is complete. Under these conditions but 1 in 12 of the impregnated ova can be carried to full term, and when pregnancy is so prolonged it produces a monster with varying degrees of abnormality. Where the pregnancy is tubal the occurrence of abnormalities in the ova may reach 96 per cent. Where there is a shortened spontaneous abortion during the first two months of pregnancy it should occasion a suspicion that there is something wrong with the ovum, which, if carried to term, may result in the birth of a monster. This is sometimes caused by abnormal implantation of the ovum in a defective or abnormal decidua, and in a mammalian ovum these abnormalities may develop before implantation occurs. From this it results that the growth and development of certain tissues in certain regions are delayed at a critical time, while other tissues not so affected grow disproportionately and the normal relationship is lost. This produces abnormality which

may destroy the fetus and bring on abortion, or may be so slight that the fetus may go on to full term, becoming some sort of monster. There is a well-marked tendency for the same mother to produce such offspring in repeated pregnancies.

A Successful Test for Liver Function in Pregnancy and its Toxemia.—ROSENFIELD and SCHNEIDERS (*Jour. Am. Med. Assn.*, March 17, 1923, **80**, 743) describe a test which they have perfected and applied to a considerable number of patients normally pregnant and also in the toxic condition. The description of the test is technically interesting to chemists. The principle upon which it is made consists in injecting a dye into a vein after removing a small quantity of blood to serve as a control. The arms are used for the experiment, very small quantities of blood are drawn from a vein in the opposite arm at intervals of fifteen minutes, one hour and two hours after injections; these various samples of blood were then studied. The chemical agent employed was phenoltetrachlorphthalein; 5 mg. of the dye for each kilogram of body weight was used. The result of this study showed that cases of normal pregnancy have a curve coinciding with that of normal non-pregnant cases. This suggested that the so-called liver of pregnancy has no actual impairment in function. Cases of toxemia including eclampsia showed a definite relationship between the degree of liver impairment as measured by this test and the degree of toxicity as shown by the clinical picture. The results obtained in several cases suggest that this test may furnish a more accurate index of the existent toxicity than variable clinical symptoms and that by this test the obstetrician may be able to anticipate the clinical picture in forming an opinion regarding the degree of toxicity present at a given time. The toxemias of pregnancy show definite liver impairment and if the toxemia be relieved there is a return of normal liver function. The test gives a quantitative index of the functional capacity of the liver and should be of service in determining the necessity for the interruption of pregnancy.

Pregnancy and Labor After the Operative Replacement of the Inverted Uterus.—TEUFIK (*Zentralbl. für Gyn.*, 1922, **46**, 1956) describes the case of a woman aged twenty-eight, whose first labor had terminated naturally. The second labor was also spontaneous, but the midwife pulled strongly upon the umbilical cord and inverted the uterus. Later the patient came to hospital, suffering from anemia and its result. The uterus was found inverted. It was replaced by Küstner's method, followed by prompt recovery. The patient left the hospital in good condition. Menstruation was regular and painless for six months after, and then the patient came to the hospital five months pregnant. She was suffering no inconvenience and was ordered an abdominal bandage and advised to abstain from violent motions. Pregnancy went on and the patient finally gave birth spontaneously to a male child fully developed at term. The placenta was also spontaneously expelled, but there was more than usual hemorrhage afterward. Mother and child made a good recovery. Spontaneous labor after inversion of the uterus and its cure by operation is of rare occurrence.

Injury in Labor to the Brain of the Newborn.—SCHWARTZ (*Zentralbl. für Gyn.*, 1922, **46**, 1965) has found that in newborn children under five months 65 per cent show some injury to the brain. These results are characteristic and typically placed and illustrate the influence of parturition upon the central nervous system. Most important are large hemorrhages into the cerebral substance and into the pia mater. When the veins are studied, instead of terminating in small branches, they end in wide blood channels in various portions of the cerebral substance. If these children survive their birth, lesions remain as the result of the hemorrhage. Areas of necrosis often develop in the brain substance. On microscopical examination, the lesions are best seen in the nerve fibers of the brain and in the axis cylinders. The whole picture is that described by Virchow as encephalitis of the newborn. So far as statistics are concerned, in 10,000 births 950 children would perish by the end of the first month. Of these 230 would show some injury to the brain, although a clinical diagnosis might have been made of asphyxia, congenital weakness, atrophy, or other condition as the essential cause of the death.

Prenatal Care.—ROBINSON and others (*Brit. Med. Jour.*, 1922, **2**, 1174) contribute their experiences upon the value of prenatal care. The mortality of the newborn arises from hemorrhage and accidents in birth, from the toxemias of pregnancy, septic infection and pre-existing or intercurrent disease. In general hospitals disease is most important; in maternities the hemorrhages and accidents of labor, and in the houses of patients septic infection. Prenatal care is most valuable in preventing toxemia, eclampsia and the accidents of labor. Routine examination during pregnancy should greatly diminish the mortality of the newborn. It was thought that such previous study of cases should reduce the application of forceps in labor to less than 3 per cent, and have a correspondingly good effect upon other conditions.

GYNECOLOGY

UNDER THE CHARGE OF

JOHN G. CLARK, M.D.,

PROFESSOR OF GYNECOLOGY IN THE UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA,

AND

FRANK B. BLOCK, M.D.,

INSTRUCTOR IN GYNECOLOGY, MEDICAL SCHOOL, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA.

Relation of Cell Type to Degree of Malignancy in Cancer of Cervix.—The hypothesis under which MARTZLOFF (*Bull. Johns Hopkins Hosp.*, 1923, **34**, 141) began his interesting study on cervical cancer was that if basal cell cancer with its relatively low grade of malignancy exists on epidermal surfaces of the body elsewhere, why should it not occur

in the cervix uteri and warrant an equally favorable prognosis? He felt that the epidermal integument of the cervix differed morphologically in no essential way from skin except for the absence of a stratum corneum, dermis, dermal glands and dermal appendages. In short, why should epidermoid cancer of the cervix differ from epidermoid cancer occurring in other situations? The object of his study, therefore, was to discover, if possible, whether in this large and common group of epidermoid or squamous cell carcinoma of the cervix the histomorphology of the predominant types of cancer cells might signify anything relating to the malignancy of the disease. Because of the relatively poor prognosis as to an eventual operative cure which can be given in these cases, it was thought that any information such an investigation might afford would be of definite value and for this purpose data were gathered from the records of 387 patients in the wards of the Johns Hopkins Hospital prior to the year 1920, including only those cases in which there were complete records together with all pathological material. The study showed that the cells seen in epidermoid cancer of the cervix fall morphologically into three large groups: transitional, fat spindle and spinal cell groups. No epidermoid cancer of the cervix was encountered which conforms to basal cell cancer of the skin in regard to its apparent lack of malignancy. The histomorphology of the predominant types of cells in epidermoid cancer of the cervix is important in that it indicates the relative malignancy of a given type of tumor. In this study the spinal cell type of cancer proved to be the least malignant, the transitional cell type is next in order of increasing malignancy and the fat spindle cell type of cancer has proved to be the most malignant of all. The adenocarcinomata, as far as relative malignancy is concerned, fall in between the spinal cell and transitional cell groups of epidermoid cancer. The presence of epithelial pearls is significant only when they are associated with cancers of the spinal cell type and then they appear to indicate a lessened malignancy of the cervical new growth. Aside from these interesting observations on histology in its relation to malignancy there were several other interesting features from a statistical standpoint which this study brought forth. For example, the vaginal mucosa was involved in over 50 per cent of all the carcinomas of the cervix in the series, irrespective of the extent of the cervical involvement. Secondary involvement of the corpus uteri in cervical cancer occurred in 41.3 per cent of the cases in which the entire length of the cervix was involved. One-third of all the patients seen during the first six months of symptomatic disease, with the exception of those suffering from the spinal cell type of cancer, had extension of the neoplastic process to the broad ligament, while less than 10 per cent of the patients with broad ligament involvement lived more than one year after operation. The first symptom of disease in almost 85 per cent of the cases was some form of unusual vaginal bleeding, while in 97 per cent of the cases some form of unusual vaginal discharge (either bleeding or leukorrhea) was the primary symptom. Of all the cancers in the series 52.1 per cent occurred between the ages of thirty-six and fifty years inclusive. Of the patients between thirty-one and thirty-five years inclusive 18.6 per cent are living and well, which is the highest "cure" incidence for any five year age-period in the study. In 58.8 per cent of the patients operated upon where broad

ligament induration was noted on physical examination, this finding signified carcinomatous extension. The total operability of the cases in this study was 46.5 per cent while the total operative mortality was 14.2 per cent. The operative mortality prevailing in their clinic at the present time however is between 6 and 7 per cent. The incidence of "cures" is almost twice as frequent in the cases treated by abdominal panhysterectomy as compared with those treated by vaginal panhysterectomy. Preliminary curettage performed several days prior to the radical operation for cancer was the procedure employed in 36.8 per cent of the patients who are now living and well. From this Martzloff concludes that a diagnostic curettage not immediately followed by a radical operation does not by any means render the prognosis hopeless. The incidence of so-called "five year cures" in this series is 26.6 per cent.

Modification of Rubin Technic for Tubal Inflation.—The modification of the Rubin technic which has been suggested by JACOBY (*Surg., Gynec. and Obst.*, 1923, **36**, 571) consists essentially in the substitution of a Janet Frank syringe for the tank of gas with its attached reducing valve and flow volumeter and the injection of air instead of oxygen or carbon dioxide. One may use any other suitable means for the introduction of air, such as a rubber bulb. The method of performing the test is as follows: With the patient in the dorsal position the bivalve speculum is introduced. The cervix and vagina are wiped dry with cotton and painted thoroughly with tincture of iodine. The cannula is introduced into the cervix past the internal os. The urethral tip on the cannula is pressed against the external os and acts as an obturator and prevents the regurgitation of gas. A tenaculum for grasping and steadying the cervix is as a rule unnecessary, for it is usually easy to introduce the cannula without it, doing away with the pain attendant on its use, and slight pressure on the cannula serves to hold the obturator firmly against the external os. The cannula is now connected by means of rubber tubing and a T-tube connection to a spring manometer on the one arm and a Janet Frank syringe with the plunger drawn out to its fullest extent on the other. Air is gently introduced through the cannula by pressure on the plunger of the syringe. The pressure exerted is recorded on the manometer. A pressure of 220 mm. mercury is the maximum permitted, and if the air will not flow at that pressure maintained for a little while, the tubes are considered closed. In such cases retests are made one or two weeks later. The usual initial pressure varies from 60 to 120 mm. mercury with a fall of pressure when the initial resistance is overcome and the air is flowing. It has been found that it is sufficient to introduce from 50 to 75 cc of air. There is no immediate reaction. Varying from a few minutes to half an hour after the patient assumes the upright position, there is a pain felt in the upper part of the abdomen and later in one or both shoulders, more commonly in the right. This pain lasts with diminishing intensity for about two days, the duration depending upon the amount of air introduced, but at no time seriously inconveniencing the patient. No other reaction occurs. This procedure has been used in 40 cases with no evidence of any serious result, such as infection. Nor is there any reason to expect it, as the result of the introduction of air, since in every

laparotomy air enters the peritoneal cavity with no untoward results. All the instruments used are of course sterilized. The advantages of this modification in technic are obvious. It eliminates the necessity of having on hand cumbersome tanks of gas with their attachments. There is no possibility of the air being exhausted, as occasionally happens with a tank when a test is in progress. Being more compact the apparatus is readily portable and there is no expense and inconvenience in the replacement of tanks. Air is free and always obtainable. The slight increase in the duration of the reaction can hardly be considered a big drawback, since it never amounts to a very great discomfort and can be regulated by the amount of air introduced.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

OSKAR KLOTZ, M.D., C.M.,

DIRECTOR OF THE PATHOLOGICAL LABORATORIES, SAO PAULO, BRAZIL,

AND

DE WAYNE G. RICHEY, B.S., M.D.,

ASSISTANT PROFESSOR OF PATHOLOGY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.

Types of Canine Anaphylaxis.—According to MANWARING, CHILCOTE and HOSEPIAN (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 274) the typical anaphylactic reaction in dogs is characterized by a sudden, pronounced fall in arterial blood-pressure which is reduced to about 25 mm. Hg, by the end of ninety seconds and is demonstrable in virtually all dogs tested from eighteen to twenty-four days after intravenous horse serum sensitization, with recovery usually in from one to two hours, depending upon the severity of the reaction. The authors have encountered another type of canine anaphylaxis, which occurred in a dog tested during the seventh week of horse serum sensitization and in which a gradual and irregular fall in the arterial pressure began four minutes after intravenous serum inoculation, death occurring in nine and one-half minutes. The lungs were found to be almost non-collapsible, but could be readily collapsed on pressure, the partial pulmonary fixation passing off in about fifteen minutes. The blood became non-coagulable by the reaction, but slight hepatic changes were observed and no duodenal hemorrhages could be seen. The picture of this latter type of reaction resembled that encountered in guinea-pig anaphylaxis.

On Isohemagglutination.—DYKE (*Brit. Jour. Exper. Path.*, 1922, **3**, 146) conducted a series of experiments consisting in the absorption of the three agglutinating sera, those of Groups II, III and IV; by the three agglutinable types of corpuscles, those of Groups I, II and III. The sera used were usually a day to a week old. The corpuscles were collected in 2 per cent sodium citrate solution in normal saline, washed

three times in normal saline and suspended in the same fluid. It was found that the age of the corpuscles made very little difference in their activity. For absorption five drops of a 50 per cent suspension of corpuscles in normal saline were added to five drops of the serum to be tested, and left standing, either overnight at room temperature, or in the incubator at 37° C. for two hours. On completion of absorption the mixture of corpuscles and serum was shaken up and centrifuged. The supernatant fluid was pipetted off and tested as to its remaining agglutinating power. The absorption tests performed on sera of Groups II, III and IV, using corpuscles of Groups I, II and III, confirmed von Dungern and Hirschfeldt's hypothesis as to the distribution and nature of agglutinins and agglutinable factors in the four blood groups. It was further found that the sera from different individuals of the same group varied in their agglutinating powers. The relative titer of the two agglutinins in any given Group IV serum may be equal or very unequal, and corpuscles from different individuals of the same group could vary as to their agglutinability by the same serum. The relative degree to which the agglutinable factors may be present in corpuscles from any individual belonging to Group I varied greatly, while corpuscles from different individuals belonging to Group I differed in this respect. As a result of his observations the author believes that a quantitative estimation of the agglutinin titer should be made before any serum is selected for grouping purposes and only those sera should be used which show agglutinating power up to a dilution of at least 1 to 10.

A Hitherto Undescribed Pair of Isoagglutination Elements in Human Beings.—Landsteiner, in 1901, discovered three human blood groups, and soon afterward, Decastelli and Sturli found the fourth group. Landsteiner recognized the existence in human serum of the presence of two isohemagglutins, and two isoagglutinable substances in the corpuscles. Recently, Guthrie and Huck reported the discovery of a third pair of isoagglutination elements. In the course of a class demonstration of the two original pairs of isoagglutination elements, as described by COCA and KLEIN (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 466), the serum of Doctor Coca—a Group I individual—was absorbed first with the washed corpuscles of a Group II person and then with the washed corpuscles of a Group III individual. The supernatant fluid, after these absorptions, no longer clumped the corpuscles of the respective Group II and Group III individuals but still possessed a vigorous power of agglutinating the corpuscles of a Group IV person, which were agglutinable by the serum of the Group II and Group III individuals. This observation indicated the presence of another pair of isoagglutination elements. Examination of ten other Group I sera revealed the presence of a new isoagglutinin in 7 of them, whereas it was present in 2 of 6 Group III sera. The possibility of this pair of isoagglutination elements being identical with that described by Guthrie and Huck must be considered as indicated by the authors.

A Dangerous "Universal Donor" Detected by the Direct Matching of Bloods.—LEVINE and MAYBEE (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 468) recount an interesting and important observation having

to do with the advisability of employing the "universal donor" Group I (Jansky) or Group IV (Moss). Their account is quoted: "In cases of transfusion where it is difficult to obtain a donor of the same group as the patient, a person of Group I (Jansky) has been considered suitable on account of the fact that the corpuscles of this group are inagglutinable by the isohemagglutinins. The fact that the plasma of a Group I individual contains isoagglutinins capable of clumping the corpuscles of the recipient has been ignored, because, under ordinary circumstances, the quantity of the plasma transfused is too small to affect the larger proportion (five to ten times) of the recipient's corpuscles. In carrying out the method of the direct matching of bloods as described by Coca, we found that the plasma of one of us (M., Group I) produced complete agglutination of ten volumes of the corpuscles of P. L. (Group II). Quantitative tests in the test tube showed that moderate agglutination of P. L. corpuscles was produced by as little as 1/20 volume of the M. plasma. This observation reveals a risk in using a member of the so-called "universal donor" group for the first time without making a rough quantitative estimation of the agglutinating power of the individual's plasma. It is advisable, therefore, in carrying out the direct matching according to Coca, to include a mixture of equal parts of undiluted recipient's citrated blood with the donor's citrated blood, diluted 1 to 5.

The Endothelial Factor in Anaphylaxis.—MANWARING, CHILCOTE and HOSEPIAN (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 273) found that if the lungs of a normal dog are perfused with Locke's solution, followed by Locke's solution containing 0.25 per cent to 1 per cent horse serum, no recognizable pulmonary reaction took place, the rate of perfusion flow remaining constant, the lungs collapsing normally on releasing the tracheal clamp and no frothy fluid escaping from trachea. If, however, the lungs of a sensitized dog were similarly perfused, a marked pulmonary reaction occurred. This reaction was characterized by a 75 per cent reduction in the rate of perfusion flow, which reached its maximum by the end of two minutes, with slight tendency to recover after three minutes; an increase in size and consistency of the lungs, with non-collapse on release of tracheal clamp and the escape of large quantities of fluid from the trachea on releasing this clamp. The authors believe that the increased capillary permeability is the most significant feature of these reactions and that 'increased specific capillary permeability will ultimately be shown to be the dominant fundamental factor in protein sensitization, to which all other anaphylactic phenomena are secondary.'

Anaphylactic Reactions on Isolated Canine Organs.—When they perfused the isolated organs of horse serum sensitized dogs with Locke's solution containing 0.5 to 1 per cent horse serum, MANWARING, CHILCOTE, and HOSEPIAN (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 282) found that there was a slight increase in perfusion resistance in the hindquarters, reducing the rate of perfusion flow about 5 per cent, but no edema; that an increased perfusion resistance occurred in the intestines, reducing the perfusion flow about 25 per cent, with increased peristaltic movements, distinct edema of intestinal wall and increased

volume of intestinal contents; that a similar perfusion resistance and edema occurred in the liver, while a still greater perfusion resistance, reducing the perfusion flow fully 75 per cent, with marked pulmonary edema, occurred in the lungs. These reactions in intestines, liver and lungs were qualitatively similar to the histamine reactions previously reported, the hindquarter reactions differing in the absence of marked edema and in the substitution of a slight vasoconstriction for the marked histamine vasodilation. The authors call attention to the fact that "if reactions similar to those observed on blood-free perfusion of isolated organs take place during anaphylactic shock in the intact animal, one can readily understand why the acute fall in arterial blood-pressure, the characteristic feature of canine anaphylaxis, does not take place in dehepatized dogs. Peripheral vasoconstriction (intestines and hindquarters) would tend to increase the arterial blood-pressure in these animals, while the reduced blood volume from edema would tend to decrease this pressure."

An Anaërobe from the Mouth Cavity of Man and Rabbits Morphologically Suggesting B. Pneumosintes.—In 1919, HOLMAN reported the isolation of a minute anaërobe out of material from the mouth of five consecutive persons not suffering from influenza. The material was cultured on cooked meat and other media and the organism attracted attention because of the abundance of gas it produced in the cooked meat, but more especially on account of its small size and the chance of its being confused in direct smears and mixed cultures with B. influenzæ. More recently, HOLMAN and KROCK (*Proc. Soc. Exper. Biol. and Med.*, 1923, **20**, 280) reported the isolation of an anaërobic bacillus from the oral cavity of four of the workers in their laboratory—an organism which they consider as identical with the five strains encountered in 1919, and with another found in an infected neck and described in 1922. The anaërobe was very small, well under 0.5 micra long, by a little less in width, being smaller than B. prodigiosus, B. bronchosepticus and B. influenzæ and about the size of B. pneumosintes. The coccoid bacillus was non-motile, Gram-negative, occurred singly, often in pairs, and in irregular groups, depending upon the medium, and was strictly and persistently anaërobic. Gas production in cooked meat medium was constant and copious and was the outstanding test tube biological feature. The bacterium passed through a Mandler filter tested against B. pyocyanous but which allowed B. prodigiosus go through under 20 pounds' pressure. The authors consider this bacterium of importance because it may be confused easily with B. pneumosintes by its morphological appearance and its manner of growth, because it is filterable through tested filters, and because it is found in the oral cavities of man and rabbits and thus could lead to confusion with B. pneumosintes from these sources. The authors further indicate that "comparable experiments to those done by Olitsky and Gates will have to be carried out to determine whether this common extremely small anaërobe will alter the blood picture after intratracheal injection, or lower the resistance of the lung to secondary invasions by other common organisms of the respiratory tract, or will show any serological or other relationship to B. pneumosintes."

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

MILTON J. ROSENAU, M.D.,

PROFESSOR OF PREVENTIVE MEDICINE AND HYGIENE, HARVARD MEDICAL SCHOOL, BOSTON, MASSACHUSETTS,

AND

GEORGE W. McCOY, M.D.,

DIRECTOR OF HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE, WASHINGTON, D. C.

Botulism. Studies on the Manner in Which the Toxin of Clostridium Botulinum Acts upon the Body. I. The Effect upon the Autonomic Nervous System.—DICKSON and SHEVKY (*Jour. Exper. Med.*, 1923, **37**, 711) believe that in botulinus intoxication in cats, dogs and rabbits there is a specific effect upon the portions of the autonomic nervous system which results in a blocking of the nerve impulses of these nerves. The experimental as well as the clinical evidence indicates that there is no damage to the nerves of the thoracicolumbar outflow. The authors state that the exact location of the damage has not been ascertained nor has the mechanism by which the nerve impulse is blocked been determined. The experiments show, however, that the lesions in these portions of the nervous system are not of central distribution but are peripheral, and the block cannot be due to an organic break in the conduction apparatus but must be due to some derangement which is relatively unstable. If it were otherwise it would not be possible to induce a physiological response even by massive stimulation, nor could the response be subsequently repeated by stimuli which lie within the limits of normal intensity. The application of the results of the experiments to the clinical manifestations of botulism will be discussed in a later report after the effect of the toxin upon the skeletal motor nerves has been described.

Experimental Observations on the Prophylaxis and Treatment of Syphilis.—NICHOLS and WALKER (*Jour. Exper. Med.*, 1923, **37**, 525) state that by inoculating the scarified surface of both sides of the scrotum of rabbits with suspensions of *Treponema pallidum*, 100 per cent of infections were obtained on one side or the other. Infection through the unbroken skin could not be produced. By gland transfers from animals with positive local inoculations, 87.5 per cent of takes were produced. These two methods were used to test the prophylactic value of 30 per cent calomel ointment. (*a*) Calomel ointment proved efficacious up to eight hours after inoculation with syphilis. (*b*) No marked difference appeared between the action of calomel in a base of lanolin and vaseline and in a base of benzoinated lard and wax. (*c*) Death from mercurial poisoning was produced in rabbits by a single application of a large amount of calomel ointment. The method of gland transfers was used to test the sterilizing effect of arsphenamine and neoarsphenamine on old infections in the rabbit. The infection was

completely abolished in every instance, whether by one, two or four intravenous doses. Natural spirochetosis of rabbits need not be a serious complicating factor in work on syphilis in rabbits, for the following reasons: (*a*) In natural spirochetosis, the lesions occur on the penis and not on the scrotum. Gland transfers are negative. (*b*) A scrotal lesion can be produced by inoculation, but it can be distinguished from that of *Treponema pallidum* infection by its course. (*c*) In studies of generalized syphilis supposed to involve the genitalia, and in sexual transmission experiments, *Treponema cuniculi* may be a serious complicating factor.

Obesity: Observations on One Thousand Cases.—PREBLE (*Boston Med. and Surg. Jour.*, 1923, **188**, 617) states that obesity is almost invariably due to bad dietary habits and not to errors in metabolism or to heredity. Overweight of 15 or more pounds is an increasingly serious condition with advancing years, conducive to heart, arterial and kidney disease, diabetes, and hypertension. Obesity is easily curable, and it is the duty of the physician to acquaint his patient and the community with the gravity of the condition and the ease with which it can be controlled.

Dengue Fever. A Clinical Report of the Galveston Epidemic of 1922.—RICE (*Am. Jour. Trop. Med.*, 1923, **31**, 73) states that the 1922 epidemic of dengue in Galveston followed a plague of yellow fever mosquitoes, and subsequently spread throughout the State. The disease presented a few characteristic features and should not be confused with other clinical entities. The rash may vary, but is distinctive. Uterine hemorrhages are common in dengue, and hemorrhages from any mucous surface may occur. Recurrences are seen, and partial immunity is of short duration, probably less than four months. The incubation period varies between four and fourteen days. Pregnancy is not disturbed. No specific treatment is known.

Weil-Felix Reaction in Rocky Mountain Spotted Fever.—KELLY (*Jour. Infect. Dis.*, 1923, **32**, 223) states that while the series of tests carried out by him is not large enough to warrant any definite conclusions, it suggests that the Weil-Felix reaction is negative in Rocky Mountain spotted fever and may be of value in differentiating between this disease and typhus fever.

Experimental Abortion in a Cow Produced by Inoculation with Bacterium Melitensis.—EVANS (*Public Health Reports*, 1923, **38**, 825) points out that *Bact. abortus* and *Bact. melitensis* are practically identical and that she has been able to cause abortion in a heifer with the latter organism.

A Report on the Indigent Migratory Consumptive in Certain Cities of the Southwest.—WHITNEY (*Public Health Reports*, 1923, **38**, 587) gives the results of an extensive study of the situation with respect to non-resident tuberculous cases in the southwestern part of the United States. It is shown that the large number of dependent or partially dependent consumptives who go to that part of the country generally

regarded as most favorable for the cure of the disease constitutes a serious financial burden on the communities to which they go. The facilities for caring for this class of cases referred to are wholly inadequate, though praiseworthy efforts are being made in many places.

The Distribution of Malaria in the United States as Indicated by Mortality Reports.—MAXCY (*Public Health Reports*, 1923, **38**, 1125) makes a careful study of the data available on his subject, and gives the following summary: "This study of mortality rates from malaria indicates that the disease is largely confined to the Coastal Plain, reaching its widest distribution in the lower Mississippi Valley. The distribution of the disease is not uniform but focal in character. Areas of high prevalence are found chiefly about the mouths of large rivers along the coast, particularly in the 'delta' lands of the Mississippi and along the valleys of its large tributaries. In Arkansas, Louisiana, Mississippi and Florida a large proportion of the total land area and population is affected by the malaria problem. In the other States in the South the problem is more or less limited to certain sections of each State, the remainder of the State being relatively or entirely free from the disease. While there has been a general decrease in incidence of the disease in the past few years, this does not hold for all parts of the country. Mortality records indicate a definite increase in incidence for the Mississippi Valley during the year 1921."

Studies on the Bio-assay of Pituitary Extracts. — SMITH and MCCLOSKEY (*Public Health Reports*, 1923, **38**, 493–512) discuss the attempts which have been made heretofore to standardize pituitary extracts and show the lack of success which has attended the efforts. The great variation in commercial preparations is shown by their own work as well as by a study of the reports of others. A method of preparing a relatively stable extract in powder form is given, together with directions for carrying out comparative tests. Several factors which might improve the activity of infundibular extract were studied, as season, sex and freezing; all of these were without serious influence. Autoclaving is destructive of the activity of the material, but fractional sterilization of acidulated extracts is harmless.

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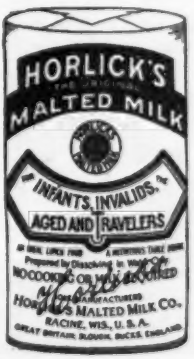

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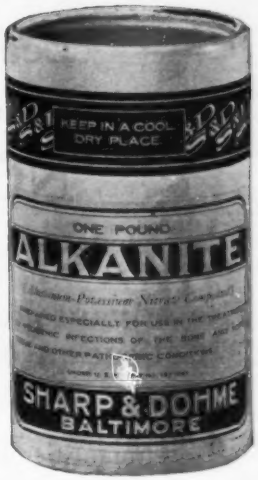

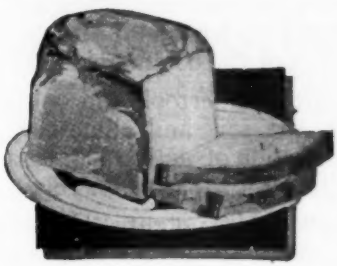

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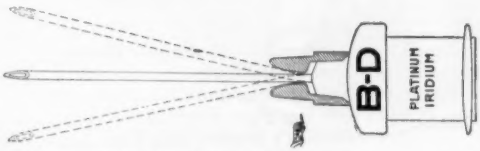

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